Chronic disease prevention: Nutrition and behavioral neuroscience approaches

Tovah Wolf
Iowa State University

Follow this and additional works at: https://lib.dr.iastate.edu/etd

Part of the Public Health Education and Promotion Commons

Recommended Citation
https://lib.dr.iastate.edu/etd/17613

This Dissertation is brought to you for free and open access by the Iowa State University Capstones, Theses and Dissertations at Iowa State University Digital Repository. It has been accepted for inclusion in Graduate Theses and Dissertations by an authorized administrator of Iowa State University Digital Repository. For more information, please contact digirep@iastate.edu.
Chronic disease prevention: Nutrition and behavioral neuroscience approaches

by

Tovah Wolf

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Nutritional Sciences

Program of Study Committee:
Lorraine Lanningham-Foster, Co-major Professor
Auriel Willette, Co-major Professor
Duck-Chul Lee
Peter Clark
John Crespi
Ruth Litchfield

The student author, whose presentation of the scholarship herein was approved by the program of study committee, is solely responsible for the content of this dissertation. The Graduate College will ensure this dissertation is globally accessible and will not permit alterations after a degree is conferred.

Iowa State University
Ames, Iowa
2019

Copyright © Tovah Wolf, 2019. All rights reserved.
# TABLE OF CONTENTS

| LIST OF FIGURES | ................................................................. | v |
| LIST OF TABLES | ................................................................. | vii |
| ACKNOWLEDGMENTS | ................................................................. | viii |
| ABSTRACT | ................................................................. | ix |
| CHAPTER 1. GENERAL INTRODUCTION | ................................................................. | 1 |
| References | ................................................................. | 3 |
| CHAPTER 2. REVIEW OF LITERATURE | ................................................................. | 5 |
| Part I: The link between insulin resistance, stress and depression: Current research and treatment | ................................................................. | 5 |
| Diabetes Diagnosis | ................................................................. | 7 |
| Stress Origins and Differences | ................................................................. | 8 |
| IR and Mood | ................................................................. | 9 |
| IR and MDD | ................................................................. | 9 |
| IR and Neural Correlates | ................................................................. | 10 |
| HPA Axis | ................................................................. | 12 |
| IR and Weight Gain | ................................................................. | 13 |
| IR Treatment: Behaviors and Mood Disorders | ................................................................. | 14 |
| Obesity and Insulin Resistance | ................................................................. | 15 |
| Diabetes and Insulin Resistance in Normal Aging: Links to Task-based fMRI Brain Activity | ................................................................. | 15 |
| Conclusion | ................................................................. | 16 |
| Part II: The role of Nutrition in Hypertension | ................................................................. | 17 |
| Potassium | ................................................................. | 19 |
| Calcium | ................................................................. | 20 |
| Magnesium | ................................................................. | 20 |
| Protein and Amino Acids | ................................................................. | 21 |
| Fiber | ................................................................. | 21 |
| Eating Patterns | ................................................................. | 22 |
| Compliance with DASH | ................................................................. | 22 |
| Counseling approaches | ................................................................. | 25 |
| Conclusion | ................................................................. | 26 |
| References | ................................................................. | 26 |
| CHAPTER 3. NEURAL, HORMONAL, AND COGNITIVE CORRELATES OF METABOLIC DYSFUNCTION AND EMOTIONAL REACTIVITY | ................................................................. | 42 |
| Abstract | ................................................................. | 42 |
| Objective | ................................................................. | 42 |
| Methods | ................................................................. | 42 |
LIST OF FIGURES

Figure 3-1: International Affective pictures system example picture scheme..................... 67
Figure 3-2: EBR magnitude changes across Time.......................................................... 68
Figure 3-3: Resting Frontal Asymmetry....................................................................... 69
Figure 3-4: Baseline Urine Cortisol............................................................................. 70
Figure 3-5: Total Arithmetic Series Correct. ............................................................... 71

Figure 4-1: Fluid Intelligence, AD risk, and Glucose. Error bars 95% confidence interval shown. Adults with no AD parental history (left graph) showed similar cognitive decline over 6 years regardless of having no diabetes or diabetes. By contrast, adults with parental family history showed (right graph) showed better fluid intelligence over time (p<0.001) in middle-age, whereas similar adults who were above 65 years of age had worse declines in fluid intelligence (p<0.01)......................................................................... 91

Figure 4-2: Diabetes, APOE4, and Anxiety UK Biobank. For anxiety, there was an APOE4 x Diabetes x Age interaction (p<0.001). Non-APOE4s (tan color) with or without diabetes showed less anxiety in aged versus middle aged. APOE4s without diabetes (left panel graph) had higher anxiety in midlife versus non-APOE4s but still showed less anxiety in late-life. APOE4s with diabetes (right graph) had less anxiety in midlife but a moderate increase in late-life. AD parental family history had a similar interaction pattern (p<0.05). .................................................................................................................. 92

Figure 4-3: Diabetes and Neural Networks UK Biobank. ............................................. 93

Figure 4-4: The graph shows face > shape contrast, AD risk, and IGF-1.BOLD signal was derived from faces > shapes trials. The brain image (A) shows the activation of the middle frontal gyri, insula and amygdala during this task. Image (B) Show those with diabetes had less activation in the amygdala. For the main effect, Figure 4-4B shows that participants with diabetes (left “blue” curve) had 1.49SD less global activation (p<0.01) in all areas compared to the controls (right “red” curve). Lower global fMRI task activity was related to higher depression (p<0.05) but not anxiety factor score. A 3-way interaction for APOE4*Age*IGF1 (p= <0.05) revealed that for example, adults with diabetes with a APOE4 genotype had a significantly lower mean in the fMRI faces shapes contrast than the group
without APOE4 (\(\bar{x}_{\text{non-APOE4}}=1.55, \bar{x}_{\text{APOE4}}=1.49; p<0.05\)), reflecting lower global activity. This trend can be seen Figure 4-4 (top graph, right graph).

Figure 5-1: Percent Change in DASH score between 1 and 9 months (n=94: 40 females, 45 males; p<0.000). The mean percent change for females was 3.42%.

Figure 5-2: DASH score at month 12 for the men (n=106).

Figure 5-3: DASH score at month 12 for the women (n=128).

Figure 5-4: Women had a higher significantly higher DASH score at month 12 (n=236: 95 females, 108 males;)

Figure 5-5: Hispanics had a significantly higher DASH score at month 9 than those who identified as not Hispanic or Latino (n=3, Hispanic/Latino: n=132, not Hispanic/Latino; p= 0.0079).

Figure 5-6: An overview of the DASH score over the course of the study (12 months) by sex, age groups, ethnicity and race.
LIST OF TABLES

Table 2-1: Adapted from diabetes.org ........................................................................................................... 7
Table 2-2: Adapted from Muntner et al., 2017 and the AHA................................................................. 18
Table 2-3: Characteristics of selected DASH Randomized Control Trials in Middle-Aged and Aged Adults ............................................................. 23
Table 3-1: Demographics and Summary Indices .......................................................................................... 65
Table 4-1: Time table of when variables of interest were collected ......................................................... 90
Table 5-1: DASH scoring table to determine DASH Score ................................................................. 111
Table 5-2: Time table of the study timeline ............................................................................................... 112
Table 5-3: Demographics of participants ..................................................................................................... 113
Table 5-4: Twelve month questionnaire participant responses (total respondents n=17) .... 114
Table 5-5: Model estimate marginal means (EMM) and SE of DASH score indices at month 12. The parameters listed in the table are also non-significant at baseline, month 3, 6, 9 and 12 and the changes between baseline and month 3, 6, 9 and 12. ................................................................................................................................. 115
ACKNOWLEDGMENTS

First off, I would like to express my utmost gratitude to my advisors, Dr. Auriel Willette and Dr. Lorraine Lannginham-Forster for giving me the opportunity to conduct research in their labs and for their mentorship. I would also like to extend my gratitude to my committee members, Dr. Ruth Litchfield, Dr. Duck-Chul Lee, Dr. Peter Clark and Dr. John Crespi for their advice and support during my graduate studies. Also, a special thank you to Jeanne Stewart for getting me acquainted and trained in at the NWRC and for her continuing advice throughout my entire graduate experience.

Thank you to those of you I had the pleasure of working with during research projects including Dr. Kesley McLimans, Dr. Angelique Brellenthin, Ashley Swanson, Dr. Maren Wolff, Dr. Nathan Meir, Chrissy Komjathy, Brandon Klinedinst, Ellie Schmidt, Tze Lam, Kate Kokemiller, Nicole Kling, Jennifer Pilut, Lisa Smith, Alexandra Voelkers, Jonathan Cerna, Abdulrazzaq Ahmed Alhendi, and Zoe Sirotiak as well as all the undergraduate and graduate students, past and present on the IBIS and CardioRACE research teams.

Thank you, Janet Johnson and Dr. Kevin Schalinske, for your mentorship and training during my teaching assistant experiences. Other FSHN staff and faculty I had also like to thank are Brenda Emery and Rose Martin. Lastly, I would like to thank Dr. Felicitas Avendano and Dr. Michael LaGier of Grand View University for their mentorship on teaching and career advice.

On a personal note, I would like to give my utmost gratitude to my husband, Ryan, for his encouragement and never-ending devotion. Words cannot describe how grateful I am to him, my parents, my in-laws, our close friends, as well as Chewie and Viggo for their continued love, and support during our career path adventures.
ABSTRACT

Chronic disease in middle-aged and aged adults in the United States continues to be on the rise. It is estimated that 60% of adults in the USA have one chronic disease and that 40% have at least two chronic diseases. The leading causes of death and disability include heart disease, cancer, chronic lung disease, stroke, Alzheimer’s disease, diabetes and chronic kidney disease. The economic burden of these diseases is estimated to be $3.3 trillion dollars in annual health care costs (CDC). It has been suggested that the key lifestyle risks for the development of chronic disease include poor nutrition, tobacco use, lack of physical activity and excessive alcohol consumption. Other risk factors include high blood pressure, diets low in fruit and vegetables and high in saturated fat and sodium.

The purpose of this dissertation is to explore nutrition and behavioral approaches to chronic disease prevention and treatment in middle-aged and aged adults by: 1) examining the relationship between insulin resistance (IR) and during a stress reactivity task, during a resting electromyography (EEG task), during a cognition task, as well as examining the differences in baseline urine cortisol levels. 2) examining the relationship between IR and functional magnetic resonance imaging (fMRI) during a stress reactivity task. 3) comparing DASH diet compliance by sex, age, race and ethnic groups among participants receiving a DASH education session at baseline and three follow-up one-on-one Dietary Approaches to Stop Hypertension (DASH) dietary counseling sessions by a Registered Dietitian Nutritionist (RDN).

The first study revealed that dysmetabolism is associated with increased emotional reactivity, predisposition toward negative affect, and specific cognitive deficits. The second study suggests that the dysmetabolism seen with insulin resistance may impact how one reacts
in stressful situations, cognition during tasks, fluid intelligence and potentially increase 
depressed mood and anxiety as well. The third study identified that one’s ethnicity, age and 
gender may effect their adherence to DASH eating. Findings of this dissertation support the 
need for additional research on IR mechanism of action to be further explored at a 
psychological, behavioral and molecular level. In addition, findings of this dissertation may 
provide insight that health professionals like RDN’s who provide DASH diet counseling with 
a motivational interviewing component, may find to be a useful intervention to increase DASH 
diet eating compliance.
CHAPTER 1. GENERAL INTRODUCTION

Chronic disease in middle-aged and aged adults in the United States continues to be on the rise with 60% of adults in the USA having one chronic disease and 40% of USA adults having at least two chronic diseases. The leading causes of death and disability include heart disease, cancer, chronic lung disease, stroke, Alzheimer’s disease, diabetes and chronic kidney disease\(^1\). The economic burden of these diseases is estimated to be $3.3 trillion dollars in annual health care costs (CDC.gov). It has been suggested that the key lifestyle risks for the development of chronic disease include tobacco use, poor nutrition, lack of physical activity and excessive alcohol consumption. Other risk factors include high blood pressure, diets low in fruits and vegetables and high in saturated fat and sodium (CDC.gov)

One in three Americans are considered obese\(^2\). Currently, 22 million adults have type 2 diabetes (T2D) and nearly 40% of middle-aged adults develop pre-type 2 diabetes\(^3\). Pre-type 2 diabetes etiology is characterized by insulin resistance (IR). Insulin is released from the pancreas after a meal is eaten to allow glucose into the cell so the body can utilize glucose for the body’s energy needs. If insulin resistance persists and worsens, either due to the inability of insulin to bind to the receptor or the signal becoming defective despite binding of insulin, glucose cannot gain entrance into the cell. This continued metabolic dysfunction will induce pre-diabetes. The pancreas compensates by releasing more insulin, but over time it cannot sustain increased insulin release to keep blood glucose levels normal and subsequently leads to the development of T2D.

T2D can promote the development of cardiovascular disease, and cardiovascular diabetes can promote T2D. Cardiovascular disease, like T2D, is currently a major public health concern around the world. One in every four deaths is attributed to heart disease,
meaning it continues to be the leading cause of death in women and men in the United States\textsuperscript{4}. The most common type of heart disease is coronary heart disease, which is estimated to kill over 370,000 Americans annually\textsuperscript{4}.

Hypertension, which has been associated with diets high in sodium as well as diets low in fiber, magnesium, and protein, are major risk factors for heart disease and stroke. It is estimated that half of American adults have hypertension\textsuperscript{5}, and that one billion people live with the disease globally\textsuperscript{6}. In 2015, it was estimated that one out of every three American adults have hypertension\textsuperscript{7} and it is estimated that one billion people globally live with the disease\textsuperscript{6}. In 2003, the Joint National Committee VII defined pre-hypertension as blood pressure with the following: systolic blood pressure levels of 120-139 mmHg and diastolic blood pressure levels of 80-89 mmHg\textsuperscript{8}. Recently, diagnosis for blood pressure has been changed and as a result an estimated 46% of Americans are now considered to have high blood pressure\textsuperscript{9}. According to the new guidelines, elevated systolic blood pressure is between 120-129 mmHg and a diastolic blood pressure less than 80 mmHg, stage I hypertension is systolic blood pressure between 130-139 mmHg or a diastolic blood pressure between 80-89 mmHg, and stage II hypertension is considered systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg. Unless life style changes and/or medication interventions are put into place, there is a risk for pre-hypertension to turn into hypertension.

Dietary Approaches to Stop Hypertension, or DASH, is a dietary approach that can prevent or lower high blood pressure\textsuperscript{11} by promoting the consumption of vegetables, fruit, nuts, seeds, beans, fat-free or low-fat dairy, whole grains, fish and poultry. The goal of DASH eating is to increase the intake of potassium, magnesium, calcium, protein and fiber. There is evidence that these nutrients aid in blood pressure control\textsuperscript{12}. For decades studies
have supported the health benefits of DASH eating. However, there has been a consistent trend for low adherence. A recent review study demonstrated that individuals with hypertension were less likely to follow DASH than individuals who did not have hypertension.10

The following chapters put forth in this dissertation seek to address these research concerns. Chapter 2 includes a review of the literature on the link between insulin resistance, depression and stress, as well as reviewing the role of nutrition in hypertension. Chapter 3 includes a journal article that examines the relationship between insulin resistance and the neural, hormonal and cognitive correlates. Chapter 4 includes a paper examining healthy aging and normal aging in a larger cohort than Chapter 3 with similar aims. Chapter 5 includes a paper examining strategies that improve DASH diet compliance to reduce the risk of heart disease in Hypertensive Individual. Lastly, Chapter 6 is a general summary and conclusions are discussed relative to the future of chronic disease prevention strategies.

References


CHAPTER 2. REVIEW OF LITERATURE

Part I: The link between insulin resistance, stress and depression: Current research and treatment

One-third of Americans are obese\(^1\), where 22 million adults have type 2 diabetes (T2D) and nearly 40\% of middle-aged adults develop pre-type 2 diabetes\(^2\). Pre-type 2 diabetes etiology is characterized by insulin resistance (IR), which is a reduced cellular response to insulin\(^3\). The concept of insulin resistance can be thought of as a lock and key. Locks, cell receptors, are on the cell surface to let energy, or glucose, into the cell, but they cannot without the key, which is insulin. Insulin is released from the pancreas after a meal is eaten to allow glucose into the cell so the body can utilize glucose for the body’s energy needs. If insulin resistance persists and and worsens, either by the inability of insulin to bind to the receptor or by defective signaling after insulin binding, glucose cannot gain entrance into the cell. This continued metabolic dysfunction that will induce pre-diabetes. The pancreas compensates by releasing more insulin, but over time it cannot sustain increased insulin release to keep blood glucose levels normal and subsequent the development of T2D occurs.

Type 2 diabetes can lead to many chronic illnesses such as heart disease, kidney disease, nerve damage, and other microvascular and macrovascular complications\(^4\). The induced damaged caused by elevated blood sugar is hypothesized to be a consequence of one of four pathways, which either cause an increase or decrease in certain metabolites in glucose metabolism\(^4\). This imbalance in metabolites can induce superoxide over-production. Superoxide is oxygen that has an unpaired electron, therefore it is reactive and can cause damage to tissues.
While it is well established that IR and T2D contribute to cardiovascular disease and other pathologies, they also adversely impact behavior. The term cognition originally came about by Cohen and colleagues carrying out studies on cognitive motivation\(^5\). According to the American Psychology Association Glossary it can be defined as “the process of knowing, including attending, remembering, and reasoning; also the content of the processes, such as concepts and memories\(^6\).”

Affective neuroscience is a behavioral science that examines neural bases of emotion and mood. A 2003 book, the “Handbook of Affective Sciences”, Davidson et al. expressed that application of the affective neuroscience theory and data to the understanding of peoples’ differences in affective style, mood disorders, and mood regulation is helping to generate a new understanding of the brain circuitry underlying these processes\(^7\).

Insulin resistance is related to deficits in cognitive\(^8\) and affective processing, particularly reactivity to psychological stress in humans\(^9\) and monkeys\(^10\). IR in euglycemic (i.e., normal blood glucose levels) or hyperglycemic (i.e., pre-type 2 diabetes and type 2 diabetes) humans is also associated with neural sequelae that impact these behavioral outcomes. It is unclear how IR affects emotional processing. It has been suggested that oxidative stress in the body, neuronal apoptosis and neuroinflammation in the brain, and the body’s electrical physical abnormalities can cause architectural changes and contribute to brain dysfunction in type 2 diabetes. This review will highlight the relationship between IR and stress, mood disorders, and the neural correlates involved. This review will also highlight research efforts put forth into treatment of these conditions.
Diabetes Diagnosis

There are several different ways a practitioner can diagnose diabetes by examining blood. Hemoglobin A1c (HbA1c) is an estimate of an average glucose level over the time span of 2 to 3 months, which measures the glycosylation of hemoglobin portion of the red blood cells. Another blood test that can be done is fasting plasma glucose. The final test that is common in the clinical setting is the Oral Glucose Tolerance Test (OGTT) which involves drinking a sugary beverage and checking blood glucose levels over 2 hours. As seen in Table 2-1, the American Diabetes Association define presence of prediabetes as a HbA1c between 5.7-6.4% or a fasting blood glucose level between 100-125 mg/dL, and not taking diabetes medications\textsuperscript{12}. The criteria for diabetes is having a HbA1c above 6.5%, a fasting blood glucose above 126 mg/dL, or taking medications that lower glucose levels\textsuperscript{12}. For OGTT, for diagnosis criteria that is at the 2-hour mark, a blood glucose level of 140-199 mg/dL for prediabetes and a blood glucose level of 200 mg/dL or higher for diabetes.

Table 2-1: Adapted from diabetes.org

<table>
<thead>
<tr>
<th>Test</th>
<th>Normal</th>
<th>Prediabetes</th>
<th>Type II Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A\textsubscript{1c}</td>
<td></td>
<td>5.7-6.4%</td>
<td>\geq 6.5%</td>
</tr>
<tr>
<td>Fasting Plasma Glucose</td>
<td>\geq 100 mg/dL</td>
<td>100 mg/dL to 125 mg/dL</td>
<td>126 mg/dL or higher</td>
</tr>
<tr>
<td>Oral Glucose Tolerance Test</td>
<td>\geq 140 mg/dL</td>
<td>140 mg/dL to 199 mg/dL</td>
<td>\geq 200 mg/dL</td>
</tr>
<tr>
<td>Random Glucose</td>
<td>N/A</td>
<td>N/A</td>
<td>\geq 200 mg/dL</td>
</tr>
</tbody>
</table>

According to the American Diabetes Association common signs and symptoms of diabetes include but are not limited to weight loss, numbness and tingling in hands and feet,
frequent urination, frequent thirst, often feeling hunger, extreme fatigue, cuts and bruises that take a long time to heal and blurry vision.

**Stress Origins and Differences**

There is substantial evidence to show that stress in the early years of life can have a lasting influence on health\(^{13-17}\). An epidemiological study that examined medical outcomes of 17,000 adults found a 1.5 to 2 times higher prevalence of early mortality, cardiovascular disease and autoimmune disorders in those who experience abuse, neglect and violence by a family member during childhood\(^{13-17}\). Children of low social economic status (SES) compared to those with higher SES showed increased rates of anxiety, attention and conduct issues, and depression\(^{18-22}\). Animal studies suggest that stress can have structural effects on the brain. In two different rat studies, the CA3 region of the hippocampus showed decreased length and branching of pyramidal apical dendrites with chronic stress and less synaptic connections\(^{23,24}\). Neural correlates will be explained in further detail later in this review.

Research suggests it is chronic stress rather than acute stress that has an influence on human physiology\(^{25-27}\). Specific life events that induce stress, such as marital separation, being a victim in a crime, or having financial problems show a causal association with depression\(^{28}\). There is substantial evidence that experiencing daily stress\(^{29-31}\), and displaying negative affect reactivity decreases with age\(^{32-34}\). Though the data are varied on whether older adults or young adults show more negative stress reactivity to daily stressors\(^{35,36}\). According to Handcock G.M & Handcock P.A., “Stress reactivity is a dynamic process involving context-dependent, interactive factors subject to person interpretation that dictate subsequent individual response patterns\(^{37}\)” Gender differences are also apparent in stress responses\(^{38}\). According to a study done in 1994 by Heuser and colleagues, using a
dexamethasone-cortisol releasing hormone test, they determined women have a higher cortisol release in comparison to men\textsuperscript{39}. Later, it was determined cortisol was 19\% higher in adult females when compared to adult males\textsuperscript{40}.

**IR and Mood**

In 2005 it was estimated approximately 18\% of the US population over the age of 18 had an anxiety disorder and 9.5\% a mood disorder\textsuperscript{41}. It has been reported that IR is related to deficits in affective processing, particularly reactivity to psychological stress in humans\textsuperscript{9} and monkeys\textsuperscript{42}. More current research shows similar results suggesting individuals with T2D had higher anxiety and depression compared to those who did not have diabetes\textsuperscript{43}. Makine et al.’s data supports that T2D individuals who are not yet on insulin, are more likely to be depressed and have negative attitudes about insulin therapy\textsuperscript{44} than non-diabetic controls. More research is needed at the behavioral and biological level that link psychological stress to the mortality and morbidity of T2D.

**IR and MDD**

IR and hyperglycemia also manifest with major depressive disorder (MDD) and several other anxiety and mood disorders. Depression is a very common mood disorder, characterized by a negative mood and loss of interest and pleasure with feelings of sadness. MDD diagnosis requires at least two or more major depressive episodes for at least two weeks and at least five of nine symptoms that cause significant impairment at work, social, or other important aspects of functioning almost every day according to the DSM-IV-TR\textsuperscript{45}. Participants with MDD showed impaired insulin sensitivity (i.e., IR) after an oral-glucose
tolerance test that was resolved after antidepressant treatment\textsuperscript{46}. Indeed, if depression is resolved, fasting glucose levels tend to improve\textsuperscript{47,48}.

An established formula, homeostatic model assessment of IR (HOMA-IR)\textsuperscript{49} is used to measure peripheral IR. A study with children who ranged 5-13 years old and who completed a self-report on the Children’s Depression Inventory at baseline, showed more depressive symptoms correlated with increasing HOMA-IR levels six years later\textsuperscript{50}. Recent meta-analyses strongly suggest that MDD\textsuperscript{51} and bipolar disorder\textsuperscript{52} are associated with higher rates of T2D. For example, individuals with T2D are twice as likely to have MDD compared to those without T2D\textsuperscript{53}. Conversely, MDD may increase the risk of developing T2D\textsuperscript{54}. Some of this increased risk of MDD, and in general stress reactivity, may be due to stigma and discrimination toward individuals who are obese\textsuperscript{55}. There is also a body of growing literature showing a genetic role in metabolic profiles and depression outcomes by analyzing specific polymorphisms\textsuperscript{56}.

**IR and Neural Correlates**

IR may be a one possible explanation underlying emotional regulation and psychopathology\textsuperscript{57–59}. For instance, mice lacking the insulin receptor exhibited increased dopamine clearance in the striatum and nucleus accumbens, leading to anxiety and depressive-like symptoms which were reversed with antidepressant treatment\textsuperscript{57}. Interestingly, long-term caloric restriction substantially reduces IR and stress reactivity in rhesus monkeys, who do not manifest bias toward obese cage mates, suggesting that the association is at least partly neurobiological in origin\textsuperscript{10,60}.

Brain regions have been examined to determine which areas are related to emotional reactivity using electroencephalogram (EEG), positron emission tomography (PET),
functional magnetic resonance imaging (fMRI) techniques. Multiple studies have shown the visual cortex being activated when viewing emotional pictures. Research using EEG, determined that frontal alpha asymmetry is a well-established biomarker of negative affect predisposition. The visual cortex has differing activation between the left and right hemisphere in response to emotional stimuli. Other brain regions showing activation include the amygdala-hippocampal region, dorsolateral prefrontal cortex, basal ganglia, ventromedial prefrontal (vPFC) and medial orbitofrontal cortex, and anterior cingulate.

Human, monkey, and rodent studies have demonstrated that IR is related to brain atrophy, as well as lower glucose uptake in the human brain. The limbic system in the body is complex and is important for many bodily functions with just a few examples being emotions, memories, and bodily drives for survival (i.e. hunger, consciousness, instincts). The hippocampus in the brain is part of the limbic system and has an important role in long-term memory and spatial memory that allows for navigation. In uncontrolled hyperglycemia diabetic rodent models analysis of neuroanatomical changes showed suppression of neurogenesis and neuronal apoptosis in the hippocampus.

A human study that used Magnetic Resonance Imaging (MRI) analysis revealed people with T2D had more hippocampal and amygdala atrophy when compared to the controls. These studies suggest that vPFC in particular is affected. This brain area is essential for top-down modulation of stress-induced emotional reactivity, as well as medial temporal areas like amygdala and hippocampus that in part grade for threat detection and emotional regulation. There are also data to support the belief that hyperglycemia accelerates brain aging and increases the risk of dementia.
HPA Axis

Many research studies support the hypothesis that chronic stress and stress inducing procedures can increase the activation of the hypothalamic-pituitary-adrenal axis (HPA axis), which has been associated with neurodegeneration, cognitive dysfunction and depression\textsuperscript{77}. An emotional stimulus can be described as something that may illicit an emotional response (i.e., seeing a hurt baby). Stress inducing stimuli, and emotional stimuli are processed by the amygdala. This activates the paraventricular nucleus and sets off a cascade of physiological responses via the release of corticotropin releasing hormone (CRH)\textsuperscript{78,79}. The adrenocorticotropic hormone (ACTH) is then released into the blood stream because CRH stimulates neurons in the anterior pituitary gland. ACTH causes the adrenal gland to release cortisol in humans. Broadly put, cortisol and glucocorticoid steroids bind to glucocorticoid receptors that are distributed throughout the human body. Glucocorticoid steroids are involved in the suppression or activation of genes which can change whether certain proteins in our body are produced or not produced\textsuperscript{80}.

A research study of six males showed that cortisol infusion can suppress insulin activities, increase blood glucose levels, and affect growth and thyroid hormones\textsuperscript{81}. When body physiology is normal, and the exposure to stress is short, feedback inhibition from the glucocorticoid will act on the HPA axis. Sustained stimulation of the HPA can cause elevated cortisol levels which can cause decreased insulin to be released from the pancreas therefore reducing the uptake and use of glucose in cells in mice, stimulating glucagon production, and in turn causing T2D\textsuperscript{82,83}. 
IR and Weight Gain

One might speculate that the start of insulin resistance contributes to further weight gain. Some suggest pathologies of excess stress may impact eating behaviors, and thus induce obesity\textsuperscript{84,85}. The majority of literature has reported that during times of stress, individuals change their eating behaviors to consume more calories rather than less calories\textsuperscript{86,87,88}. Evidence exists that individuals who are overweight are more likely to gain weight in response to stress than those who are of a normal weight\textsuperscript{88}. Stress can induce corticoid steroid release which can increase one’s appetite for food\textsuperscript{89}, but stress can also lead to a decrease in food intake\textsuperscript{90}. Increased insulin levels can be induced by stress which in turn has been shown to decrease food intake\textsuperscript{91}. Insulin and leptin receptors are present in the brain neurons that help sustain energy by governing food intake\textsuperscript{92}. Other examples of signaling molecules involved are cholecystokinin and tumor necrosis factors, as well as lipids and sugars that can impact the hypothalamus but also limbic and autonomic brain regions.

Psychological influences, for instance excess calorie consumption, may override the effects of insulin and leptin receptors by higher-level brain functions of the frontal cortex and limbic brain\textsuperscript{93}, which may impact an individual’s weight status\textsuperscript{94}. For example, there was an unusual study using a mouse model that looked at the role of dominance and subordinance on T2D and metabolic syndrome. The dominant mice ate roughly the same amount of a high fat diet as the subordinates, but results showed that chronic subordination led to increased weight gain and increased glucose intolerance and insulin resistance\textsuperscript{95}, illustrating the possibility of psychosocial stress impacting IR.
IR Treatment: Behaviors and Mood Disorders

In streptozotocin (STZ) diabetic induced rats, behavioral training improved insulin signaling in the hippocampus\textsuperscript{96}. Induced diabetic mice, also by STZ, had impaired water maze navigation and hippocampal long-term potential when compared to controls and the latter was only partially restored after insulin treatment\textsuperscript{97}. Kemp and colleagues used an insulin sensitizer medication and determined that it reduced depression in individuals with abdominal obesity\textsuperscript{98}. Twelve weeks after an initiation dose of 15 mg, which was later titrated per patient tolerability at week 4, the Inventory of Depression Symptomology (IDS) decreased by 21.2 ±1.8 (p<.001). When they removed outliers, they also saw a decrease in insulin resistance correlated with improved depression severity (r=0.46)\textsuperscript{98}.

Recently, a different group of researchers concluded that after 12 weeks of human participants taking an intranasal insulin, it had no effect on improving mood or markers of cognition. Though they did note that 12 weeks may not have been sufficient time\textsuperscript{99}. Anti-diabetes medication Rosiglitazone administered for only four weeks in mice showed improvements in cognition and reduced depression-like behaviors in mice subject to chronic stress as well as reduced blood glucose and oxidative and inflammatory biomarkers\textsuperscript{100}.

There is currently no cure for diabetes, but substantial evidence exists that gastric bypass surgery can reverse T2D\textsuperscript{101,102} and increase psychometric cognitive function\textsuperscript{103}, but due to the possible consequences of surgery and its malabsorptive nature, there are several contradictions. That is why IR mechanisms of action need to be further explored, at a psychological, behavioral and molecular level so that prevention and treatment methods can be more effectively utilized.
**Obesity and Insulin Resistance**

Although the exact causes of insulin resistance are not completely understood, scientists think the major contributors to insulin resistance are excess weight and physical inactivity. Studies that examine human plasma show that excess macronutrients in the adipose tissues stimulates release of inflammatory mediators such as tumor necrosis factor α and interleukin 6 (IL-6), and reduces production of adiponectin\textsuperscript{104} predisposing to a pro-inflammatory state and oxidative stress\textsuperscript{105}. The increased level of IL-6 stimulates the liver to produce and secrete C-reactive protein. Increased levels of IL-6 and C-reactive protein increase the risk of developing T2D in varying populations\textsuperscript{106}. Inflammation is a contributing mechanism for the development of cardiovascular diseases including atherosclerosis, insulin resistance, metabolic syndrome, and diabetes mellitus\textsuperscript{106,107}. Complications of insulin resistance long term and co-morbid conditions include hypoglycemia, hypertension, dyslipidemia, increased cardiovascular disease death rates, increased heart attack rates, stroke, blindness and eye problems, kidney disease, and amputations\textsuperscript{2}. Other causes of insulin resistance may include ethnicity; certain diseases; hormones; steroid use; other medications; older age; sleep problems, especially sleep apnea; and cigarette smoking\textsuperscript{2}.

**Diabetes and Insulin Resistance in Normal Aging: Links to Task-based fMRI Brain Activity**

Studies have shown that IR and diabetes impact executive function and task based fMRI studies have focused on attention or working memory\textsuperscript{108}. Most other research paradigms focus on food salience in obese subjects\textsuperscript{109}. In aging, quantitative reviews and meta-analyses indicate that 40% of adults with diabetes manifest anxiety\textsuperscript{110} and are twice as likely to have clinical depression\textsuperscript{53}. 
IR may also directly induce this negative affect\(^\text{111}\). For instance, lipopolysaccharide injections in healthy men aged 18 to 65 years old led to endotoxemia-induced peripheral inflammation and IR, where IR mediated increases in energy-conserving behaviors like anxiety, depression, and irritability, as well as memory deficits\(^\text{112–114}\). These studies had small sample sizes and the cognitive effects vary in the literature. Comparatively, little work has been done on emotion regulation, reactivity, or negative affect. During an angry and fearful face versus shapes task, obese adults had less activity in hippocampus, amygdala, and inferior temporal cortex\(^\text{115}\). In addition, less amygdala activity was related to more negative affect\(^\text{115}\). While other studies have examined IR\(^\text{116}\) and fasting versus elevated blood glucose on fMRI affect tasks\(^\text{117}\).

**Conclusion**

This review implies that IR may be a mechanism that could manipulate emotional regulation. Over time, IR can lead to type 2 diabetes if diet, physical activity, and medical treatment cannot improve the condition. Other research suggests that positive affect can lead to improved physical\(^\text{118}\) and mental health\(^\text{119}\). Social support is also an important factor in health outcomes\(^\text{120}\) and that social isolation can lead to early mortality and morbidity of chronic disease\(^\text{121,122}\).

The obesity epidemic in this country, and globally, is clearly multi-factorial. This review does not encompass all the possible factors that may contribute to the continuing obesity epidemic and in turn, pre-diabetes. Not only is this a continuing health concern, but it has an economic burden on the country as well. In 2012, it was estimated that in excess of $322 billion USD were spent on general medical costs for diabetes treatment (diabetes.org).
More research is needed to establish if adults with T2D and IR are related to psychophysiological and behavioral measures of psychological stress reactivity, or negative affect predisposition. Clinical studies that monitor IR throughout the treatment of mood disorders would be beneficial to explore as well. If decreased insulin resistance could manipulate emotional regulation to lead to more positive affect, health goals may become more easily obtainable.

**Part II: The role of Nutrition in Hypertension**

Cardiovascular disease is currently a major public health concern around the world. Historically, the diagnostic criteria for hypertension\textsuperscript{123} required at least two blood pressure readings on separate days of a systolic blood pressure \( \geq 140 \) millimeter of mercury (mmHg), a diastolic blood pressure \( \geq 90 \) mmHG or use of blood pressure lowering medication. In 2015, it was estimated that one out of every three American adults had hypertension\textsuperscript{123} and it was estimated that one billion people globally had the disease\textsuperscript{124}. In 2003, the Joint National Committee VII defined pre-hypertension as blood pressure with the following: systolic blood pressure levels of 120-139 mmHg and diastolic blood pressure levels of 80-89 mmHg\textsuperscript{125}. However, recently the diagnosis for blood pressure has been changed, which means that it is now estimated 47% of Americans are considered to have high blood pressure\textsuperscript{126}. According to the new guidelines, elevated systolic blood pressure is between 120-129 mmHg and a diastolic blood pressure less than 80 mmHg. Stage I hypertension is systolic blood pressure between 130-139 mmHg or a diastolic blood pressure between 80-89 mmHg, and stage II hypertension is considered systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg. Muntner et al.\textsuperscript{127}, proposes “the 2017 ACC/AHA hypertension guideline has the potential to increase hypertension awareness, encourage lifestyle
modification and focus antihypertensive medication initiation and intensification on US adults with high CVD risk." These guidelines can be viewed in Table 2-2.

Table 2-2: Adapted from Muntner et al., 2017\textsuperscript{127} and the AHA.

<table>
<thead>
<tr>
<th>Blood Pressure Categories American Heart Association*</th>
<th>Systolic mm Hg</th>
<th>Diastolic mm Hg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt; 120</td>
<td>and 80</td>
</tr>
<tr>
<td>Elevated</td>
<td>120 – 129</td>
<td>and &lt; 80</td>
</tr>
<tr>
<td>High Blood Pressure Stage 1</td>
<td>130 – 139</td>
<td>or 80 - 89</td>
</tr>
<tr>
<td>High Blood Pressure Stage 2</td>
<td>≥ 140</td>
<td>or ≥ 90</td>
</tr>
<tr>
<td>Hypertensive Crisis</td>
<td>&gt; 180</td>
<td>and/or &gt; 120</td>
</tr>
</tbody>
</table>

Lifestyle changes and/or medication interventions are needed to prevent hypertension. Without implementation of one or both of these interventions, there is a high risk that pre-hypertension can turn into hypertension. Hypertension, which has been associated with diets high in sodium\textsuperscript{128–130}, is a risk factor for heart disease and stroke. Longitudinal and review data supports positive associations between hypertension and risk of stroke, coronary heart disease, congestive heart failure, peripheral vascular disease, and renal failure\textsuperscript{131–134}.

Epidemiological studies show a positive relationship between excess sodium consumption and blood pressure. An extremely large study performed includes the International Study of Macro/Micronutrients and blood pressure (INTERMAP), which is an international cross-sectional epidemiology study consisting of 4,680 men and women between 40 and 59 years old form China, Japan, the United Kingdom, and the United States. A potential shortcoming for epidemiological studies is that sodium intake may differ more within individuals than between individuals. This measurement error diminishes the statistical power to detect significant associations between sodium intake and cardiovascular
outcomes\textsuperscript{135}. Randomized control studies have also demonstrated the link between decreased sodium intake and blood pressure reduction in hypertensive and non-hypertensive adults\textsuperscript{136–139}, though sodium specifically will not be the focus of this review.

This review will focus on other specific nutrients and their role in potentially affecting blood pressure as well as counseling approaches used in attempts to implement dietary changes to reduce hypertension. Dietary Approaches to Stop Hypertension, or DASH, is a dietary approach that can prevent or lower high blood pressure\textsuperscript{140} by promoting the consumption of vegetables, fruit, nuts, seeds, beans, fat-free or low-fat dairy, whole grains, fish and poultry. The goal of DASH eating is to increase the intake of potassium, magnesium, calcium, protein and fiber. There is strong evidence that suggests these nutrients aid in blood pressure control\textsuperscript{141}.

**Potassium**

Potassium is the dominant intracellular ion in the human body found in all human cells essential for regulation of blood flow. In brief, potassium exerts its vasodilatation control when skeletal muscle is activated, this causes the muscle cell to release potassium, which in turn stimulates the Na-K pump in the vascular smooth muscle cells (VSMC). VSMC malfunction contributes to the pathogenesis of hypertension, atherosclerosis and other vascular diseases. Due to the uneven pumping of sodium and potassium, the cells hyperpolarize causing reduced flow of calcium into the VSMCs leading to the arteriole dilating, hence increased blood flow\textsuperscript{142}. Potassium also exerts its dilating effect by increasing the uptake of norepinephrine in the post-synaptic nerve terminals\textsuperscript{143,144}.

A meta-analysis that includes 25 research studies suggests that those who supplement with potassium to meet the adequate intake of 90 mmol/day, especially those with high
sodium intake not on medication and not meeting potassium requirements, had decreased blood pressure\textsuperscript{145}.

**Calcium**

Calcium/calmodulin dependent phosphorylation of the myosin light chain prompts vascular smooth muscle contraction. Myogenic tone and reactivity are thought to be affected by calcium influx through L-type calcium channels\textsuperscript{146}. The voltage gated vascular calcium channels are regulated by a variety of systems that seem to be triggered by vasoconstrictors, and in turn cause the g-protein couple receptors to be triggered, specifically Gq/11/G12/13 for instances stimulated by norepinephrine\textsuperscript{147}. A study using a knock-out mouse model of L-type 1.2 calcium channel significantly reduced mean arterial blood pressure from 120 ± 4.5 to 87 ± 8 mmHg. A meta-analysis examined 9 dietary studies versus 33 non-dietary inventions e.g. a calcium supplement. Though there was greater blood pressure reduction in the dietary trials, it was not significantly different than the non-dietary interventions\textsuperscript{148} suggesting there may be similar reductions in blood pressure whether calcium in coming through food sources or a calcium supplement.

**Magnesium**

Magnesium is a calcium channel antagonist, therefore promoting vasodilation agents which result in the vasodilation of VSMC. Unlike calcium, it is predominately located intracellularly. Small alterations in the concentrations of magnesium inside or outside of cells have meaningful impacts on vascular tone, reactivity, contractility, growth ability and cardiac excitability\textsuperscript{149,150}. 
Hypertensive individuals not on blood pressure lowering medication show reduced levels of magnesium\textsuperscript{151,152}. In reviewing magnesium supplementation for human subjects, supplementation can be effective in some subgroups of people. A subset of hypertensive Black participants who have low levels of magnesium and are being treated with diuretics can receive blood pressure lowering effects of magnesium if supplemented long-term\textsuperscript{153,154}.

**Protein and Amino Acids**

A study that used rats showed a low protein maternal diet induced high blood pressure in the offspring, but could be reversed with glycine supplementation given to the male and female offspring\textsuperscript{155}. However, it is currently unknown if it is increased protein or decreased carbohydrate intake that affects blood pressure. In a cross-over feeding trial, partial substitution of carbohydrate with either protein or monounsaturated fat lowered blood pressure and improved HDL, LDL, triglycerides, and total cholesterol\textsuperscript{156}. A review study that compared the difference between animal and plant protein in 46 studies concluded there is not enough substantial nor mechanistic evidence to draw a conclusion at this time\textsuperscript{157}. However, the observational literature is leaning toward plant protein having more of an inverse relationship with blood pressure than for animal protein.

**Fiber**

The link between dietary fiber and blood pressure has been examined in observational studies in general populations\textsuperscript{158,159}. When one looks across cultures, those who have plant-based diets, for instance, rural Asia, Africa, New Guinea and Pacific Islands, historically tend to have reduced blood pressure compared to omnivores that reside in industrialized societies\textsuperscript{160,161}, where fiber consumption on average is low. As individuals
migrate to more industrialized societies, hypertension prevalence tends to increase\textsuperscript{162}. Diets with increased intake of fiber can reduce energy intake and influence weight and satiation\textsuperscript{163,164}. A few clinical studies did not support a significant effect of dietary fiber on lowering blood pressure\textsuperscript{165–167}, which illustrates that it is challenging to link blood pressure control to a single nutrient or single food group.

**Eating Patterns**

According to the American Heart Association, diets that are plentiful in vegetables, fruits, whole grains, fish, seeds, nuts and legumes and people that choose low fat dairy products, some meatless meals, and foods low in sodium and saturated fat have been shown to decrease the risk of heart disease, especially with the combination of being physically active. A study that used a comparative risk assessment estimated that 45.4% of US deaths caused by stroke, T2D and stroke in 2012 were attributable to poor health habits\textsuperscript{168}. These poor dietary habits included low intake of vegetables and fruit, nuts and seafood compared to high consumption of sugar sweetened beverages, processed meats and sodium\textsuperscript{168}.

**Compliance with DASH**

A well-established area of research uses observational studies focusing on the link between high sodium diets and hypertension\textsuperscript{128,169,170}. For decades studies have supported the health benefits of DASH eating. However, there has been a consistent trend for low adherence. A recent review study demonstrated that individuals with hypertension were less likely to follow DASH than individuals who did not have hypertension\textsuperscript{171}. Table 2-3 on the following pages illustrates selected DASH randomized control trials in middle-aged and aged adults.
Table 2-3: Characteristics of selected DASH Randomized Control Trials in Middle-Aged and Aged Adults

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Type of RCT</th>
<th>Sample Size</th>
<th>Duration</th>
<th>Sex</th>
<th>Mean Age</th>
<th>Intervention description</th>
<th>BP outcomes</th>
<th>DASH compliance assessment technique</th>
<th>DASH compliance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Booth et al., 2003(^{172})</td>
<td>Parallel</td>
<td>54</td>
<td>12</td>
<td>44 males</td>
<td>47.7</td>
<td>Counseling 1. DASH + Weight loss 2. Low fat diet</td>
<td>Change in BP from baseline: 1. -7.6/-5.4 2. -2.1/-1.0</td>
<td>% of subjects meeting specified food group targets: Fruit Vegetables Dairy</td>
<td>67% 48% 21%</td>
</tr>
<tr>
<td>Epstein et al., 2012(^{273})</td>
<td>Parallel</td>
<td>144</td>
<td>16</td>
<td>96 females 48 males</td>
<td>67</td>
<td>Counseling 1. DASH + Weight loss 2. DASH 3. Usual Diet</td>
<td>Change in BP from baseline: 1. -16.1/-9.9 2. -11.2/-7.5 3. -3.4/-3.8</td>
<td>Composite DASH adherence score 6.24 (max score of 10)</td>
<td></td>
</tr>
<tr>
<td>Nowson et al., 2009(^{274})</td>
<td>Parallel</td>
<td>95</td>
<td>14</td>
<td>95 females</td>
<td>60 58.4</td>
<td>Counseling</td>
<td>Change in BP from baseline:</td>
<td>24-hour urinary excretion: Sodium Potassium Decrease 20%. Increased 50%. Increased by 23 ± 9 mmol/d</td>
<td>Sodium decreased (38.6 ± 6.9 mmol/d) Potassium increased (6.9 ± 3.6 mmol/d)</td>
</tr>
<tr>
<td>Nowson et al., 2004(^{275})</td>
<td>Cross-over</td>
<td>94</td>
<td>11</td>
<td>37 females 57 males</td>
<td>55.6</td>
<td>Counseling 1. Low sodium, Low calcium Diet 2. DASH diet 3. Low sodium, high potassium diet 4. High calcium Diet</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2-3 continued.

<table>
<thead>
<tr>
<th>Author and Year</th>
<th>Type of RCT</th>
<th>Sample Size</th>
<th>Duration</th>
<th>Sex</th>
<th>Mean Age</th>
<th>Intervention description</th>
<th>BP outcomes</th>
<th>DASH compliance assessment technique</th>
<th>DASH compliance level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obarzanek et al., 2007</td>
<td>Parallel</td>
<td>782</td>
<td>72</td>
<td>50 females 50 males</td>
<td>62</td>
<td>Counseling 1. Established 2. Established + DASH 3. Advice Control</td>
<td>1.8.6/6 2. -9.5/-6.2 3. -7.4/-5.2</td>
<td>Sodium Potassium Phosphorus DASH adherence Index</td>
<td>Decreased (24.5 mmol/d) Increased (9.6 mmol/d) Increased (10.7 mmol/d) Increased of 0.9 in score (0-1 indicated adherence to the DASH dietary pattern)</td>
</tr>
<tr>
<td>Racine et al., 2011</td>
<td>Parallel</td>
<td>147</td>
<td>52</td>
<td>122 females 25 males</td>
<td>72.5</td>
<td>Counseling 1. MNT 2. Information</td>
<td>N/A</td>
<td>DASH Score</td>
<td>1.85 (max of 9)</td>
</tr>
<tr>
<td>Troyer et al., 2010</td>
<td>Parallel</td>
<td>210</td>
<td>52</td>
<td>174 females 36 males</td>
<td>&gt;60</td>
<td>Counseling and meal provision: 1. Received meal 2. Not Received meal</td>
<td>N/A</td>
<td>DASH Score</td>
<td>2.1 (max score of 9)</td>
</tr>
<tr>
<td>et al., 1999</td>
<td>Parallel</td>
<td>459</td>
<td>11</td>
<td>216 females 243 males</td>
<td>45</td>
<td>Feeding Trial: 1. Control Diet 2. Increased fruit &amp; vegetable (F/V) 3. Combination/DASH</td>
<td>ΔF/V – ΔControl (p&lt;0.0001). -2.8/-1.1 ΔDASH- ΔControl (p&lt;0.0001). -5.5/-3.0</td>
<td>Body weight Urinary excretion: Sodium Potassium Phosphorus Urea Nitrogen Daily adherence score Anonymous post survey</td>
<td>Maintained Unchanged Increased Increased ~0 (zero indicated no deviation from study diet) 96.5% of subjects reported always or usually ate all of the study foods</td>
</tr>
</tbody>
</table>

Abbreviations: DASH, Dietary Approaches to stop Hypertension; Maximum, max; N/A, non-applicable; Δ, change; ~, approximately;
Counseling approaches

Studies have been conducted on lifestyle counseling approaches to help treat hypertension, but few are specific to the type of counseling method used\textsuperscript{180}. Pignone and colleagues published a review study that ranked studies to promote healthy interventions at being a high, moderate or low level of counseling interventions administered by nurses, doctors, registered dietitians, nurse practitioner or master’s in public health\textsuperscript{181}. Their results showed that moderate or high levels of counseling interventions including use of interactive health communications tools via computer and/or telephone increased the intake of fruits and vegetables and decreased intake of saturated fats across 21 trials that were reviewed\textsuperscript{181}. The high intensity studies in this review often had well-trained counselors, often with dietitians or nutritionists providing the nutrition counseling\textsuperscript{181}.

Another study revealed 16 out of 58 individuals who received 30 to 60 minutes of dietary counseling with a nutritionist achieved a 5 to 9\% weight loss and had a significantly lower odds ratio to increase antihypertensive medication when compared to the control group\textsuperscript{182}. A pilot study that combined Mediterranean diet counseling by a nutritionist and stress management techniques counseling by a psychologist for 16 individuals in the intervention group had significant decreases in systolic and diastolic blood pressure when compared to the 20 individuals in the control group\textsuperscript{183}. More specifically, a team of researchers developed a lifestyle modification program specific to DASH eating via mobile health\textsuperscript{184}. Its usability is currently being researched, but with the flexibility of mobile health technologies it may have the potential to promote behavior change in hypertensive individuals.
Conclusion

Cardiovascular disease continues to be the leading cause of death in the United States. As can be concluded from the review above, randomized control studies and epidemiological studies in blood pressure control need to continue due to the increase in heart disease prevalence. A “one glove fits all” approach is not possible due to genetic, cultural and environmental factors. Implementation of DASH eating can significantly decrease systolic and diastolic blood pressure\textsuperscript{185} by highlighting the combination of nutrients and consuming foods in their whole form that can have an impact on blood pressure. It is interesting to note, that regardless of sodium intake, implementing DASH eating significantly decreased systolic and diastolic blood pressure within 30 days in studies that did not include an exercise intervention\textsuperscript{185}. Therefore, promoting the consumption of a variety of foods may have a meaningful impact on helping combat heart disease.

References


43. van Dooren FEP, Denollet J, Verhey FRJ, et al. Psychological and personality factors in type 2 diabetes mellitus, presenting the rationale and exploratory results from The


with increased recurrence of depressive episodes and rapid response to antidepressant

Insulin resistance in brain alters dopamine turnover and causes behavioral disorders.
2015;(36). doi:10.1073/pnas.1500877112

Cerebral Glucose Uptake in Late Middle-Aged Adults at Risk for Alzheimer Disease.

59. Willette AA, Modanlo N, Kapogiannis D. Insulin Resistance Predicts Medial
Temporal Hypermetabolism in Mild Cognitive Impairment Conversion to Alzheimer
Disease. Diabetes. 2015;64(6):1933-1940. doi:10.2337/db14-1507

60. Willette AA, Coe CL, Colman RJ, et al. Calorie Restriction reduced psychological
stress and reactivity and its association with brain volume and microstructure in aged

doi:10.1016/j.neuroimage.2004.03.028

Technical Manual and Affective Ratings Lang, P.J., Bradley, M.M., & Cuthbert, B.N.

63. Coan JA, Allen JJB. Frontal EEG asymmetry as a moderator and mediator of

64. Jackson DC, Mueller CJ, Dolski I, et al. Now you feel it, now you don’t: Front brain
electrical asymmetry and individual differences in emotion regulation. Psychol Sci.


doi:10.1111/1469-8986.3520199

emotion dimensions in the prefrontal cortex—an fMRI study. Neuroimage.


CHAPTER 3. NEURAL, HORMONAL, AND COGNITIVE CORRELATES OF METABOLIC DYSFUNCTION AND EMOTIONAL REACTIVITY

Modified from a paper that was published in Psychosomatic Medicine.

Tovah Wolf, M.S1, Vera Tsenkova, Ph.D.2, Carol D. Ryff, Ph.D2,3, Richard J. Davidson, Ph.D2,3,4,5, Auriel A. Willette, Ph.D1,6,7,8

1Department of Food Science and Human Nutrition, Iowa State University, Ames, IA, United States.
2Institute on Aging, University of Wisconsin-Madison, Madison, WI, United States.
3Department of Psychology, University of Wisconsin-Madison, Madison, WI, United States.
4Center for Healthy Minds, University of Wisconsin-Madison, Madison, WI, United States.
5Waisman Laboratory for Brain Imaging and Behavior, University of Wisconsin-Madison, Madison, WI, United States.
6Department of Psychology, Iowa State University, Ames, IA, United States.
7Department of Biomedical Sciences, Iowa State University, Ames, IA, United States.
8Department of Neurology, University of Iowa, Iowa City, IA, United States.

Abstract

Objective

Pre-diabetes and type 2 diabetes (i.e., hyperglycemia) are characterized by insulin resistance (IR). These problems with energy metabolism may exacerbate emotional reactivity to negatively valenced stimuli and related phenomena like predisposition toward negative affect, as well as cognitive deficits. Higher emotional reactivity is seen with hyperglycemia and IR. Yet, it is largely unknown how metabolic dysfunction correlates with related neural, hormonal, and cognitive outcomes.

Methods

Among 331 adults from the Midlife in the United States (MIDUS), we cross-sectionally examined eye-blink response (EBR) to gauge reactivity to negative, positive, or neutrally-valenced pictures from international affect picture system (IAPS) stimuli proximal to an acoustic startle probe. Increased EBR to negative stimuli was considered an index of stress reactivity. Frontal alpha asymmetry, a biomarker of negative affect predisposition, was determined using resting electroencephalography (EEG). Baseline urinary cortisol output was
collected. Cognitive performance was gauged using the Brief Test of Adult Cognition by telephone (BTACT). Fasting glucose and insulin characterized hyperglycemia or the homeostatic model assessment of IR (HOMA-IR).

Results

Higher HOMA-IR corresponded to an increased startle response, measured by EBR magnitude, for negative versus positive stimuli [R²=0.218, F(1,457)=5.48, p=.020, euglycemia: Mean±SD=.092±.776, hyperglycemia: Mean±SD=.120±.881]. Participants with hyperglycemia vs. euglycemia showed greater right frontal alpha asymmetry [F(1,307)=6.62, p=.011, euglycemia: Mean±SD=.018±.167, hyperglycemia: Mean±SD=.029±.160] and worse BTACT arithmetic performance [F(1,284)=4.25, p=.040, euglycemia: Mean±SD=2.390±1.526, hyperglycemia: Mean±SD=1.920±1.462]. Baseline urinary cortisol (log10 μg/12 hr) was also dysregulated in individuals with hyperglycemia [[F(1,324)=5.09, p=.025, euglycemia: Mean±SD=1.052±.332, hyperglycemia: Mean±SD=.961±.362].

Conclusion

These results suggest that dysmetabolism is associated with increased emotional reactivity, predisposition toward negative affect, and specific cognitive deficits.

Acronyms: BTACT = Brief Test of Adult Cognition by telephone; EBR = Eye-blink response; EEG = electroencephalography; EMG = electromyography; HOMA-IR (log10) = Homeostatic model assessment of insulin resistance (logarithm base 10); IAPS = International Affective Picture System; IR = insulin resistance; MDD = major depressive disorder; Pre-T2D = Pre-type 2 diabetes; T2D = Type-2 diabetes; WHR = waist-hip-ratio
Introduction

One-third of Americans are obese\(^1\), where 22 million adults have type 2 diabetes and nearly 40% of middle-aged adults develop pre-type 2 diabetes\(^2\). Pre-type 2 diabetes etiology is characterized by insulin resistance (IR), which is a reduced cellular response to insulin\(^3\). While it is well established that IR and type 2 diabetes contribute to cardiovascular disease and other pathologies, they also impact behavior. For example, IR is related to deficits in cognitive\(^4\) and affective processing, particularly reactivity to psychological stress in humans\(^5\) and monkeys\(^6\). IR in euglycemic or hyperglycemic (i.e., pre-type 2 diabetes and type 2 diabetes) participants is also associated with neural sequelae that impact these behavioral outcomes\(^7,8,9\). It is unclear how IR affects cognitive and emotional processing. It has been suggested that oxidative stress, neuronal apoptosis, neuroinflammation, and electrophysiological abnormalities can cause architectural changes and contribute to brain dysfunction in type 2 diabetes\(^10\).

IR and hyperglycemia also manifest with major depressive disorder (MDD) and several other anxiety and mood disorders. Participants with MDD showed impaired insulin sensitivity (i.e., IR) after an oral-glucose tolerance test that was resolved after antidepressant treatment\(^11\). Indeed, if depression is resolved, fasting glucose levels tend to improve\(^12,13\). Recent meta-analyses suggest that MDD\(^14\) and bipolar disorder\(^15\) are associated with higher rates of type 2 diabetes. For example, individuals with type 2 diabetes are twice as likely to have MDD\(^16\) and impaired cognitive performance\(^17,18\) compared to those without type 2 diabetes. Conversely, MDD may increase the risk of developing type 2 diabetes\(^19\). Some of this increased risk of MDD, and in general emotional reactivity, may be due to stigma and discrimination toward individuals who are obese\(^20\). However, IR may be a critical biological mechanism underlying emotional reactivity and psychopathology\(^9,21,22\). It is chronic stress
rather than acute stress that has an influence on human physiology\textsuperscript{23–25}. Animal studies show chronic stress leads to low-grade chronic inflammation in the brain\textsuperscript{26}, resulting in macrophage infiltration in the gut that can induce metabolic dysfunction\textsuperscript{27}.

Thus, it is important to further investigate biological, psychological, and neural correlates examining associations between behavioral reactivity and metabolic dysfunction. The International Affective Picture System (IAPS) is commonly used for experimental investigation of emotion and attention. Brain regions have been examined in regards to which areas are associated with emotional reactivity. Multiple studies have shown the visual cortex being activated when viewing emotional pictures\textsuperscript{28,29}. The visual cortex has differing activation between the left and right hemisphere in response to emotional stimuli\textsuperscript{30,31}. Other brain regions showing activation include the amygdala-hippocampal region\textsuperscript{28}, dorsolateral prefrontal cortex\textsuperscript{32}, basal ganglia\textsuperscript{28}, ventromedial prefrontal (vPFC) and medial orbitofrontal cortex\textsuperscript{28}, and anterior cingulate\textsuperscript{28,32}. Human\textsuperscript{21,22,33,34} and monkey\textsuperscript{8} studies have demonstrated that IR is related to brain atrophy, as well as less glucose uptake in humans\textsuperscript{35}, in most of these areas but particularly vPFC\textsuperscript{22}. The vPFC is essential for top-down modulation of stress-induced emotional reactivity, as well as medial temporal areas like amygdala and hippocampus that in part grade for threat detection and emotional regulation\textsuperscript{36}.

One method of examining emotional reactivity is the eyeblink startle response, which is an involuntary periorbital eye reflex to a typically loud acoustic stimulus. Vrana and colleagues\textsuperscript{37} initially found that pairing a startle probe with an aversive or pleasant stimulus respectively facilitated or inhibited the automatic eyeblink response, allowing assessment of state and trait affective disposition as well as emotional reactivity\textsuperscript{38,39}. IAPS have been commonly used as a primary or foreground stimulus paired with acoustic startle\textsuperscript{40}. It is also
the case that emotion-modulated startle varies based on when IAPS stimuli are presented. For example, Larson and co-workers found that startle modulation of the eyeblink response disappears 4-7 seconds after a given picture disappears from the screen\textsuperscript{41}, suggesting that examining early versus late eyeblink startle response may help better distinguish affect facilitation or inhibition versus a response just due to the startle probe.

Despite associations between stress reactivity and metabolic dysfunction, a full understanding of how this relates to the startle eyeblink response and other neural correlates remains unknown. Therefore, it was worthwhile to determine in otherwise healthy, middle-aged adults if hyperglycemia and IR were related to psychophysiological and behavioral measures of psychological emotional reactivity, or negative affect predisposition. Our central hypothesis is metabolic dysfunction is related to neural biomarkers of emotional reactivity. By using electromyography (EMG) and electroencephalogram (EEG) data from the MIDUS (Midlife in the United States) study\textsuperscript{42}, differences between healthy adults and those with IR and pre-type 2 diabetes or type 2 diabetes (i.e., hyperglycemia) can be identified. In this study, we investigated if hyperglycemia and IR were associated with: 1) worse cognitive performance and dysregulated cortisol; and 2) higher psychophysiological measures of emotional reactivity, both at rest and during picture presentation paired with acoustic startle using eye-blink response (EBR).

**Research and Design Methods**

**Participants**

The data for this study was obtained from the MIDUS database (www.midus.wisc.edu/midus2). MIDUS II is a cross-sectional study that started in 2002 which was a follow up to the original MIDUS I study launched in 1995. The follow up study was completed by 2009 and included a collection of neuroscience data in a subset of 331
respondents from 1,255 MIDUS participants who were part of the biomarker project within the study. The MIDUS protocols were reviewed by the University of Wisconsin-Madison Institutional Review Board. All participants signed verbal consent for the biomarker project and gave verbal consent for the telephone and mail survey data before the initiation of the study. Participants were excluded from the analysis if biomarker data was missing, or if 2 of 3 EBR measurements were missing. Among the participants with biomarker data, there were no significant differences between age, sex, income level or marital status. However, Love et al. indicated that compared to the larger MIDUS sample from which they were drawn, the biomarker participants had significantly higher educational levels, with 52.2% attending high school/some college, and 42.1% being a college graduate or beyond. The sample also was predominately white (78.3%), and 13.8% of responders reported that they smoke cigarettes.

**Biological Measures**

As described in the MIDUS protocol, fasting blood samples were collected during an overnight stay. Cobas Integra Systems assay (Roche Diagnostics, Indianapolis, USA) was used to measure glycated hemoglobin (HbA1c) with an inter-assay CV of the control 1.1-3.4%, an intra-assay CV of 0.43%, and a reference range of 4.0-5.6%. An enzymatic assay photometrically measured fasting glucose (Roche Modular Analytics P, Indianapolis, USA) and an ADVIA Centaur Insulin immunoassay (Siemens, Malvern, USA) was used to measure fasting insulin. Insulin inter-assay CV of the control was 2.4-4.6%, an intra-assay CV of 2.5-4.0%, and a reference range of 4-27 uIU/mL. Glucose inter-assay CV of the control was 1%, an intra-assay CV of 1%, and a reference range of 70-99 mg/dL. An established formula was used to calculate homeostatic model assessment of IR (HOMA-IR), which is used to measure peripheral IR. Urine was collected over 12 hours to measure neuroendocrine
hormones like cortisol and creatinine, which were isolated using high-performance liquid chromatography - mass spectrometry.

**Determination of Hyperglycemia (Pre-Type 2 Diabetes, Type 2 Diabetes)**

Current criteria from the American Diabetes Association were used to define presence of prediabetes (HbA1c between 5.7-6.5% or glucose between 100-126 mg/dL, and not taking diabetes medications) and diabetes (HbA1c above 6.5%, fasting glucose above 126 mg/dL, or taking medications that lower glucose levels such as Metformin)\(^4^6\).

**Affective Neuroscience Assessments**

The neuroscience project of MIDUS II investigated emotional reactivity and recovery by obtaining EMG data and EBR magnitude and amplitude in response to 90 IAPS pictures of 30 positive, 30 neutral or 30 negative emotional valence using EMG29. Please see Figure 3-1 for an illustration of stimulus presentation. Facial muscle recordings like EBR provide differential facets of emotional response stemming from processing emotional stimuli\(^4^7,4^8\). EBR provides objective estimates of time, magnitude, and amplitude of emotional response during and following IAPS.

For the EBR scoring, EBR magnitudes were calculated by subtracting the amount of integrated EMG at reflex onset from that at peak amplitude (maximum amount of integrated EMG between 20 and 120 ms following probe onset). Trials with no detected EBR were assigned a magnitude of zero and included in the analysis. EBR magnitudes were log-transformed to normalize the data, then z-scored to range-correct the data separately for each participant. A participant’s data was excluded when the participant did not respond with a detectable EBR on less than 75% of the total number of probes. EBR amplitudes were
calculated similarly, except trials with no detectable eyeblink reflex were excluded from the analysis.49

After accounting for missing EBR and HOMA-IR data, our analysis included approximately 123 euglycemia, 89 pre-type 2 diabetes, and 44 type 2 diabetes individuals. EBR is an objective index of the startle response. The human startle response is commonly used in research studies and in clinical practice to measure central nervous system activity and EMG is frequently used to obtain it. EBR in response to acoustic startle stimuli was measured by placing two mini electrodes below the eye. The pictures shown to the participants were from the IAPS. For a given trial, the acoustic startle stimuli (105 dB) was administered for 50ms during one of three phases: 1) The “early” phase at 2,900ms after picture onset while the picture was on the screen to assess reactivity; 2) the “middle” phase at 400ms after picture onset; and 3) the “late” phase at 1,900ms after picture offset and removal to assess longer-term recovery (Figure 3-1). Schaefer et al. showed across all valences that EBR at a 2nd “middle” phase probe occurring 400ms after picture offset had decreased magnitude, which suggested that pre-pulse inhibition may have affected the 2nd probe magnitude due to close temporal proximity to the picture offset. Taking their finding into consideration, we dropped this time point from our analysis.

Electroencephalography

EEG data were also collected to assess scalp electrical activity and thereby indirectly assess cortical brain activity. A geodesic electrode net on the scalp with 128 channels of EEG was used to collect the data (www.egi.com). Resting frontal asymmetry was defined as the difference between the right and left side prefrontal cortex activation, as measured by EEG. Higher activation of the left side of the prefrontal cortex compared to the right is related to a
predisposition toward positive affect\textsuperscript{52}, whereas higher activation of the right side of the prefrontal cortex compared to the left is associated with predisposition toward negative affect\textsuperscript{48}. This is gauged using Alpha wave frequency. Resting EEG asymmetry was collected before image presentation. To constrain type 1 error, we focused on alpha wave output comparing the f3/f4 and f7/f8 channels, which have been used to assess right frontal asymmetry\textsuperscript{52}.

**Cognitive Assessment**

Part of the Brief Test of Adult Cognition by telephone (BTACT) included a number completion series and a category fluency task. Accuracy and total number correct of 1 thru 5 numbers series tasks were recorded and the number of unique words mentioned in a particular category in 15 seconds. Number series tests have been used to measure fluid intelligence and reasoning\textsuperscript{53}.

**Statistics**

All analyses were conducted using SPSS 23 (IBM Corp, New York, USA). Fasting labs, including glucose, insulin and HOMA-IR were log transformed to produce a normal distribution. Restricted maximum likelihood linear mixed models were used to analyze the main effects or interactions of HOMA-IR or hyperglycemia on EBR during the early vs. late phase of IAPS stimulus presentation for the following contrasts: 1) negative minus positive; and 2) negative minus neutral. Covariates include age, sex, and waist:hip ratio\textsuperscript{54–56}. The same model was used to predict resting frontal EEG asymmetry, as well as cognition and cortisol output during the arithmetic task. One subject had predictor values greater than 3 standard
deviations from the mean and was excluded from analysis. Significance was determined as p<.05.

Results

Data Summary

Table 3-1 lists demographics, HOMA-IR, EEG, EBR, and other baseline sample characteristics, as well as comparisons between the euglycemia versus hyperglycemia groups.

EMG EBR startle reflex

For EBR startle reflex magnitude, there was a HOMA-IR x Trial Phase interaction [F(1,457)=5.48, p=.020], indicating that HOMA-IR differentially predicted EBR for various trial phases. Specifically, higher HOMA-IR corresponded to an increased startle response for negative relative to positive stimuli [R2=.218, p<.001] (Figure 3-2), but not during the late phase after the image disappeared (Figure 3-3). For EBR startle reflex amplitude, participants with pre-type 2 diabetes and type 2 diabetes were more responsive for negative relative to neutral stimuli during early picture onset than euglycemic participants [F(1, 290)=4.06, p=.045].

EEG frontal asymmetry

For resting EEG, subjects with pre-type 2 diabetes or type 2 diabetes had lower alpha wave output in right versus left frontal areas including f3/f4 [F(1,307)=6.62, p=.011] (Figure 3-4) and f7/f8 [F(1,307)=5.99, p=.015] (Euglycemia Mean±SEM: .0007±.0064;
Hyperglycemia Mean±SEM: -0.0210±.0062), which reflects greater right frontal activity. Higher log HOMA-IR was not related to f3/f4 output [p=.310] but was modestly associated with greater f7/f8 right frontal asymmetry [R2=.030, p=.002].

**Basal Cortisol**

At baseline, a main effect for cortisol urine output showed that baseline urinary cortisol was lower in type 2 diabetes and pre-type 2 diabetes participants compared to those with normal blood glucose levels [F(1,324)=5.09, p=.025] (Figure 3-4). Similarly, higher HOMA-IR was related to lower baseline urine cortisol corrected for creatine [F(1,324)=9.27 p=.003].

**Cognitive Assessment**

Participants with pre-type 2 diabetes or type 2 diabetes showed lower total performance scores on the arithmetic task than those with euglycemia [F(1,284)=4.25, p=.040] (Figure 3-5). Lower repetition scores on the BTACT category fluency task was not related to glycemic status [F(1,286)=1.27, p=.282].

**Discussion**

Our results suggest that some degree of metabolic dysfunction is related to brain-based emotional reactivity, urinary cortisol levels, and cognitive function. Individuals with pre-type 2 diabetes and type 2 diabetes showed a heightened startle-related stress response to negative versus positive stimuli during picture presentation, but not after picture offset during the recovery period. These results suggest that IR predicts heightened early stress response for “unpleasant” vs. “pleasant” emotional stimuli. It has been previously shown that IR is
related to deficits in cognitive and affective processing among rhesus monkeys\textsuperscript{8} and humans\textsuperscript{5}. The link between stress and insulin is not clear and requires further investigation. Long-term calorie restriction substantially reduces IR and stress reactivity in rhesus monkeys, who do not manifest bias toward obese cage mates, suggesting that the association is at least partly neurobiological in origin\textsuperscript{7,8}. It is interesting to note that calorie restriction in aged rhesus monkeys reduces IR, emotional reactivity to novel stressors, and related neurodegeneration in the vPFC and hippocampus without affecting activity or attention behavior\textsuperscript{6,8}.

This suggests that weight loss and lower IR may reduce emotional reactivity. It should be noted that WHR was covaried in this report’s statistical models, suggesting variance related to weight or adiposity may not be directly affecting associations with IR and glycemic status.

Alternatively, the start of IR could contribute to further weight gain. Pathologies of excess stress may impact eating behaviors, and thus induce obesity\textsuperscript{57,58}. Most studies have reported that during times of stress, individuals change their eating behaviors to consume more calories rather than less calories\textsuperscript{59,60,61}. Indeed, individuals who are overweight are more likely to gain weight in response to stress than those who are of a normal weight\textsuperscript{61}. Stress can induce corticosteroids, which can increase one’s appetite for food\textsuperscript{62}, but stress can also lead to a decrease in food intake\textsuperscript{63}. Increased insulin levels can be induced by stress, which in turn has been shown to decrease food intake\textsuperscript{64}. Insulin and leptin receptors in the arcuate nucleus of the hypothalamus help sustain energy by governing food intake\textsuperscript{65}. Other examples of signaling molecules involved are cholecystokinin\textsuperscript{66} and tumor necrosis factors\textsuperscript{67}, as well as lipids\textsuperscript{68} and sugars that can impact the hypothalamus but also limbic and
autonomic brain regions. Some individuals may be predisposed to IR due to epigenetics and genetics. For instance, the fat mass and obesity-related gene (FTO) has been associated with obesity, with an approximately 0.4 kg/m² rise in BMI correlated with each copy of a specific allele.

Our study also observed modestly dysregulated cortisol output due to hyperglycemia, suggesting dysregulation of the hypothalamic-pituitary-adrenal axis underlying stress perception and response. Abraham et al. similarly found weak to moderate associations between metabolic dysfunction markers, cortisol, and self-reported stress. Another study showed individuals with type 2 diabetes had flattened cortisol during the day compared to others in the study who did not have type 2 diabetes. The authors suggested individuals with type 2 diabetes showed heightened cortisol levels in the evening when they would normally decline. Regardless, hyperglycemia has been related to increased anxiety and depression scores using measures like the Patient Health Questionnaire (PHQ-9) and the Generalized Anxiety disorder scale (GAD-7).

Resting EEG confirmed our EBR findings, where greater right frontal asymmetry was seen in pre-type 2 diabetes and type 2 diabetes. This is a well-established neural biomarker associated with predisposition toward negative affect. Makine et al. similarly found that individuals with type 2 diabetes who are not yet on insulin were more likely to be depressed and have negative attitudes about insulin therapy than non-diabetic controls. Our EEG results showed very modest associations with HOMA-IR compared to pre-type 2 diabetes and type 2 diabetes, suggesting that overt metabolic disease such as type 2 diabetes, but not relatively mild dysfunction such as IR, may be related to a neurobiological predisposition to
focus on negative affect. More research is needed at the behavioral and biological level that link psychological stress to type 2 diabetes related morbidity.

Our study found that individuals with type 2 diabetes and pre-type 2 diabetes scored worse on a math task than euglycemic individuals. There is strong evidence to suggest that type 2 diabetes is related to worse cognitive performance, possibly due to greater atrophy, white matter lesions, and infarcts in subcortical brain regions related to executive processes. It would be useful to see if deficits in glucose metabolism or lower brain volume mediate these associations.

This study has several limitations and strengths. The participants of the MIDUS study live in a U.S. geographical region that was predominantly white, so it may not be representative of the entire U.S. population. Additionally, the relationships were specific to glycemic status or IR, where hyperglycemia and hyperinsulinemia have overlapping but specific effects on neural function such as memory formation. Since this study is correlational in nature, it cannot be ruled that relationships we found are causal. Longitudinal data acquired in MIDUS or other cohorts may help to establish more causal relationships. Specifically, data collected over time could help strengthen our understanding of whether variation in IR over time predicts subsequent changes in emotional reactivity, urinary cortisol, and cognitive performance or whether these correlates predict possible subsequent changes in IR. A strength of this research includes the large sample size, robust statistical methods, and the consistency of our findings with the existing literature.

The relationship of HOMA-IR with the biological facets of emotional reactivity should prompt more research to uncover underlying mechanisms. This study provides evidence that metabolic dysfunction may be related to the tendency to react more strongly to
negative stimuli, and to increase frontal neural asymmetry, a biological measure that has been used to gauge predisposition of part of prefrontal cortex to attend to negative stimuli. This implies that metabolic dysfunction may be a potential mechanism that could partly modulate emotional reactivity to negative stimuli. Positive affect can lead to improved physical and mental health\textsuperscript{79}, and lifestyle interventions can prevent and delay type 2 diabetes for people at risk more than metformin\textsuperscript{80}. IR mechanisms of action need to be further explored at a psychological, behavioral and molecular level, to determine if prevention and treatment methods can be utilized to improve cognitive function, emotional reactivity to negative stimuli, and more broadly affective predisposition.

**Acknowledgements**

This study was funded in part by the College of Human Sciences at Iowa State University, a Big Data Brain Initiative grant through the Iowa State University Office of Vice President for Research, NIH grant AG047282, and the Alzheimer's Association Research Grant to Promote Diversity grant AARGD-17-529552. The data used in the preparation of this article were obtained from the MIDUS database (http://midus.wisc.edu). As such, the investigators within MIDUS contributed to the design and implementation of MIDUS and/or provided data but they did not participate in analysis or writing of this report. University of Wisconsin-Madison, University of California-Los Angeles and Georgetown University clinical research centers helped conduct this study. MIDUS is funded by the National Institute on Aging (PO1-AG020166; Carol D. Ryff, Principal Investigator). John D. Catherine and Catherine T. MacArthur of the Foundation Research Network on Successful Midlife Development were the supporters of the original project. The authors also thank
Ashley Swanson and Kelsey McLimans of Iowa State University for their comments on an earlier version of this manuscript, McKenzie E. Besch and Ellie L. Schmidt of Iowa State University for assistance with data collation and Brandon Klinedinst for his advice on statistical revisions.

Author contributions: T.W. researched the data, analyzed the data, and wrote the manuscript. A.A.W., V.T., C.D.R., and R.J.D. offered expertise and reviewed and edited the manuscript. A.A.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The data in this article was included in an abstract session at Experimental Biology 2016 and 2017.

References


58. Sinha R, Jastreboff AM. Stress as a Common Risk Factor for Obesity and Addiction Obesity and Addiction: The Integral Role of Stress. Biol Psychiatry. 2013;73(Figure 1):827-835. doi:10.1016/j.biopsych.2013.01.032


Metabolic dysfunction in this paper refers to a dysfunction of metabolism, pertaining to either an irregular blood sugar lab value, an irregular cortisol lab value or inflammation.

1 Metabolic dysfunction in this paper refers to a dysfunction of metabolism, pertaining to either an irregular blood sugar lab value, an irregular cortisol lab value or inflammation.
### Tables and Figures

#### Table 3-1: Demographics and Summary Indices

<table>
<thead>
<tr>
<th></th>
<th>Euglycemic (n=150)</th>
<th>Pre-Type 2 Diabetes (n=109)</th>
<th>Type 2 Diabetes (n=65)</th>
<th>All Participants (n=324)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>50.55 ± 0.87</td>
<td>53.33 ± 1.05</td>
<td>58.35 ± 1.45</td>
<td>53.05 ± 0.63</td>
</tr>
<tr>
<td><strong>Sex (F,M) (n)</strong></td>
<td>89,61</td>
<td>54,55</td>
<td>38,27</td>
<td>181,143</td>
</tr>
<tr>
<td><strong>Currently Smoking</strong></td>
<td>21</td>
<td>16</td>
<td>12</td>
<td>49</td>
</tr>
<tr>
<td><strong>On glucose lowering</strong></td>
<td>0⁰a</td>
<td>0⁰a</td>
<td>40⁰b</td>
<td>40</td>
</tr>
<tr>
<td><strong>BMIm²</strong></td>
<td>28.82 ± 0.54</td>
<td>31.08 ± 0.60</td>
<td>33.13 ± 0.88</td>
<td>30.45 ± 0.38</td>
</tr>
<tr>
<td><strong>WHR</strong></td>
<td>0.88⁰a ± 0.01</td>
<td>0.91⁰a ± 0.01</td>
<td>0.94⁰b ± 0.01</td>
<td>0.90 ± 0.01</td>
</tr>
<tr>
<td><strong>HOMA-IR (log10)</strong></td>
<td>0.30 ± 0.03⁰a</td>
<td>0.52 ± 0.03⁰b</td>
<td>0.74 ± 0.05⁰c</td>
<td>0.44 ± 0.02</td>
</tr>
<tr>
<td><strong>Urine Cortisol</strong></td>
<td>1.06 ± 0.03</td>
<td>0.97 ± 0.03</td>
<td>0.93 ± 0.05</td>
<td>1.00 ± 0.02</td>
</tr>
<tr>
<td><strong>EEG F3/F4</strong></td>
<td>0.02 ± 0.01</td>
<td>-0.04 ± 0.02</td>
<td>-0.01 ± 0.02</td>
<td>-0.01 ± 0.01</td>
</tr>
<tr>
<td><strong>HbA1c %</strong></td>
<td>5.61 ± 0.02⁰a</td>
<td>6.00 ± 0.04⁰a</td>
<td>7.81 ± 0.24⁰b</td>
<td>6.17 ± 0.07</td>
</tr>
<tr>
<td><strong>EBR Mag (Avg Negative z-score)</strong></td>
<td>0.01 ± 0.03</td>
<td>0.07 ± 0.04</td>
<td>0.07 ± 0.05</td>
<td>0.04 ± 0.02</td>
</tr>
<tr>
<td><strong>EBR Mag (Avg Neutral z-score)</strong></td>
<td>-0.01 ± 0.03</td>
<td>-0.05 ± 0.04</td>
<td>-0.01 ± 0.05</td>
<td>-0.03 ± 0.02</td>
</tr>
<tr>
<td><strong>EBR Mag (Avg Positive z-score)</strong></td>
<td>-0.04 ± 0.03</td>
<td>-0.06 ± 0.03</td>
<td>-0.01 ± 0.04</td>
<td>-0.04 ± 0.02</td>
</tr>
<tr>
<td><strong>EBR Amp (Avg Negative z-score)</strong></td>
<td>0.04 ± 0.02</td>
<td>0.02 ± 0.02</td>
<td>0.03 ± 0.03</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td><strong>EBR Amp (Avg Neutral z-score)</strong></td>
<td>0.04 ± 0.02</td>
<td>0.04 ± 0.02</td>
<td>0.02 ± 0.03</td>
<td>0.03 ± 0.01</td>
</tr>
<tr>
<td><strong>EBR Amp (Avg Positive z-score)</strong></td>
<td>-0.06²a ± 0.02</td>
<td>-0.04 ± 0.02</td>
<td>-0.03²b ± 0.03</td>
<td>-0.05 ± 0.01</td>
</tr>
</tbody>
</table>

Abbreviations: SD = standard deviation; Amp = amplitude; Avg = average; EBR = eye-blink response; EEG = electroencephalography; HOMA-IR (log10) = homeostatic model assessment of insulin resistance (logarithm
base 10); Mag = magnitude; WHR, waist-hip-ratio. Variables are shown as mean ± standard error of the mean or frequency count. Superscript letters per row indicate a significant difference of one sub-group versus another sub-group with a different superscript letter, based on a MANOVA with a Sidak post-hoc testing. For example, the type 2 diabetes, pre-diabetes, and euglycemic groups each have a significantly different mean value versus the other groups. For EBR Magnitude (Avg Positive), euglycemic and type 2 diabetes groups differ, whereas the pre-diabetes group shows no difference versus either.
Figure 3-1: International Affective pictures system example picture scheme.
Figure 3-2: EBR magnitude changes across Time. EBR as predicted by HOMA-IR. The Mean EBR magnitude reflects the differences between the “pleasant” and “unpleasant” images during either the early or late phase of the picture presentation. EBR reflex on magnitude in μV was measured during either the early phase (i.e., 2900ms after picture appears) or late phase (i.e., 1900ms after picture disappears). EBR signal was log-transformed to normalize data, then z-scored per subject to control for the large individual differences that often occur with EMG. *** = p < .001. Covariates included age, sex, HOMA-IR, WHR, and diabetes status. HOMA-IR (log10), Homeostatic model assessment of insulin resistance log transformed; EBR, Eye-blink response.
Figure 3-3: Resting Frontal Asymmetry. Differences in R vs. L frontal EEG alpha power magnitude among individuals with euglycemia or hyperglycemia. Data are means ± SD. Covariates included age, sex, and WHR. EEG, electroencephalography; L, left; R, right; μV2; microvolts squared; F, frontal; SD, standard deviation; T2D, type 2 diabetes; WHR, waist-hip-ratio.
Figure 3-4: Baseline Urine Cortisol. Differences in baseline urine cortisol (log10 μg/12 hr) adjusted for creatinine among participants with euglycemia or hyperglycemia. Data are means ± SD. Covariates included age, sex and diabetes status. μg, microgram; g, gram; T2D, type 2 diabetes; log10, logarithm base 10; SD, standard deviation.
Figure 3-5: Total Arithmetic Series Correct. Differences in total arithmetic series answers correct among participants with euglycemia and or hyperglycemia. Data are means ± SD. Covariates included age, sex, and diabetes status. T2D, type 2 diabetes; SD, standard deviation.
CHAPTER 4. METABOLIC DYSFUNCTION IN A UK MIDDLE-AGED AND AGED COHORT

Tovah Wolf\textsuperscript{1}, Brandon Klinedist\textsuperscript{1}, Colleen Pappas\textsuperscript{1}, Kelsey McLimans\textsuperscript{1}, Qian Wang\textsuperscript{1}, Auriel A. Willette\textsuperscript{1,2,3,4}

\textsuperscript{1}Department of Food Science and Human Nutrition, Iowa State University, Ames, IA, United States.
\textsuperscript{2}Department of Psychology, Iowa State University, Ames, IA, United States.
\textsuperscript{3}Department of Biomedical Sciences, Iowa State University, Ames, IA, United States.
\textsuperscript{4}Department of Neurology, University of Iowa, Iowa City, IA, United States.

Abstract

Background

Type 2 diabetes and pre-diabetes rates in the United States and in other industrialized countries around the world continue to be on the rise. There remains a need for research on how metabolic dysfunction, like insulin resistance are related to neural and cognitive outcomes.

Objective

To examine diabetes, IR and healthy aging by age groups can be compared to assess if there are relationships to fMRI activity during induction or regulation to determine if there are links to depression, anxiety, fluid intelligence, and negative effect.
Methods

The UK (United Kingdom) Biobank is an observational study that is community-based and includes roughly 500,000 individuals. This report includes 1623 women, and 1496 men (aged 47 to 81 years old).

Results

Associations between metabolic dysfunction, genetic AD risk, and glucose levels were found. Adults with parental family history showed markedly better fluid intelligence over time (p<.001) in middle-age, whereas similar adults who were above 65 years of age had worse declines in fluid intelligence (p<.01). Age corresponded to lower depression (p<.001) and anxiety (p<.05) Z-scores of 0.02SD and 0.002SD. T2D was linked to a 0.2SD higher depression score (p<.001). Regarding depression, an Age × Diabetes interaction (p<.001) association showed that adults with diabetes relative to no diabetes had higher depression scores in middle aged (+0.44SD) and the aged (+0.17SD). For anxiety APOE4 × Diabetes × Age interaction (p<.001).

For preliminary resting state fMRI data, in default mode network (DMN), among adults with no AD parental history, having diabetes compared to no diabetes was linked to less DMN strength in middle and late-life. By contrast, in adults with AD parental history diabetes in middle compared to late-life was related to 1.5SD more versus 2SD less DMN strength.

Fearful or angry faces versus shapes trials induced activity in areas involved in threat detection, affect salience, and “top-down” affect. Participants with diabetes had 1.49SD less global activation). And adults with diabetes with a APOE4 genotype had a significantly lower mean in the fMRI faces shapes contrast than the group without APOE4 (x̅ non-APOE4=1.55, x̅ APOE4=1.49; p<.05).
Conclusion

These results suggest that dysmetabolism, such as T2D, is associated with increased negative affect, decrease fluid intelligence, increased depression and less default mode network strength.

Introduction

Type 2 diabetes (T2D) and insulin resistance (IR), the progressive inability of insulin to regulate glucose, which can lead to cognitive decline, late-onset Alzheimer’s disease (AD) pathology, and higher AD risk\textsuperscript{1-10}. This continues to be a large public health issue because 25% of adults over 65 years old have diabetes and up to 60% have clinically significant IR\textsuperscript{11}. By 2050, it is projected that 33% of aged adults may develop diabetes due to rising obesity rates\textsuperscript{12}.

It is also known that diabetes and IR are related to neuropsychiatric disturbances such as impaired emotional regulation, depression, and anxiety. In normal aging, rigorous quantitative reviews and meta-analyses indicate that 40% of adults with diabetes manifest anxiety\textsuperscript{13} and are twice as likely to have clinical depression\textsuperscript{14}. IR may also directly induce negative affect\textsuperscript{15}. For example, lipopolysaccharide injections in healthy men aged 18 to 65 years old lead to endotoxemia-induced peripheral inflammation and IR, where IR mediates increases in energy-conserving behaviors like depression, anxiety and irritability, as well as memory deficits\textsuperscript{16-18}. However, these studies had small sample sizes, and cognitive effects are varied in the literature.

IR is a feature of Alzheimer’s Disease (AD) that can occur without diabetes. For instance, there is noticeable IR in the hippocampus of post-mortem amnestic Mild Cognitive Impairment (MCI) and AD brains, correlating strongly with worse memory and global
cognition before death in adults without diabetes\textsuperscript{19}. Conversely, intranasal insulin or “healthy lifestyle” therapies may slow memory decline depending on genetic factors\textsuperscript{20,21,22}.

Research supports that neuropsychiatric disturbances are AD risk factors\textsuperscript{23}, and in MCI and AD are just as informative as cognitive decline in tracking disease onset and progression. For instance, it is estimated that about 45\% of hospitalized MCI and 80\% of AD patients exhibit neuropsychiatric disturbances that worsen with disease progression\textsuperscript{24–26}. Furthermore, AD participants with versus without AD show more depressive affect and apathy\textsuperscript{27}. It has been suggested that metabolic dysfunction may serve as a common neurobiological marker or mechanism underlying emotional disturbances and cognitive decline, as diabetes and IR influence many similar brain regions and white matter tracts that underlie these behaviors\textsuperscript{24}.

Diabetes studies that have used animal models with AD to extend human findings and suggest possible brain areas of interest to examine. To begin, increased depressive and anxiety like behaviors occur in insulin receptor\textsuperscript{28} or Macrophage inhibitory factor (MIF)\textsuperscript{29} knock-outs, db/db mutants\textsuperscript{30}, mice given antagonists against insulin sensitizing Peroxisome proliferator-activated receptor gamma (PPAR\textgreek{g})\textsuperscript{31}, and Apolipoprotein E $\varepsilon$4 (APOE4) knock-ins with diet-induced high glucose\textsuperscript{32}. This emotional dysfunction is tied to IR in the periphery and brain, including hippocampus, amygdala, striatum, and other areas critical for emotion regulation\textsuperscript{33} and learning and memory\textsuperscript{34}. Therapeutically, neuronal insulin sensitizing agents\textsuperscript{35} extenuating chronic stress induced cognitive impairment and negative affect. Further, intranasal insulin in wild type mice can reduce anxiety and enhance cognitive function in the absence of disease\textsuperscript{36}. Finally, AD mouse models also display anxiety-like
behaviors, where calorie restriction lowers peripheral and brain IR and leads to decreased anxiety and less AD pathology in hippocampus\textsuperscript{37,38}.

For middle-aged (aged 40 to 65 years old) or aged (>65 years old) cognitively normal adults with AD genetic risk factors a group recently termed Preclinical AD\textsuperscript{39}, having diabetes/high glucose or IR does not merely add to total AD risk. While having diabetes or 1 APOE4 allele each typically doubles AD risk, having both factors synergistically promotes a 6 to 10 times greater risk for AD\textsuperscript{39–41}. Though it should be mentioned that estimates vary based on ethnicity, race, and physical activity. AD parental family history typically triples risk\textsuperscript{42–44}, where interactions with diabetes and APOE4 gene alleles, are unknown.

These interaction effects extend to cognitive decline. For example, among cognitively normal adults aged 50 to 98 years old, only APOE4 carriers with diabetes had significant declines in global, memory, and executive function domains, as well as more AD-specific neurofibrillary tangles and senile plaques in hippocampus\textsuperscript{45–47}. Other studies show that greater cognitive decline occurs with diabetes or higher glucose among APOE4 carriers in cognitively intact middle to aged adults or in MCI\textsuperscript{48,49}. However, some reports find no combination effects between APOE4 and metabolic factors like IR on cognitive decline\textsuperscript{50}, such as Lyall et al.\textsuperscript{51} that found no such effects in over 100,000 UK Biobank participants. Testing these interactions in the context of age, which is the strongest risk factor for AD as well as cognitive decline, may clarify these mixed findings in the literature. In this study, we investigated if metabolic dysfunction, such as diabetes or having one or two copies of the APOE4 genotype, related to worst negative affect and cognition and in preclinical AD, MCI and AD versus normal aging.
Research and Design Methods

Participants and Variables

Baseline data was downloaded for 14,971 UK Biobank participants aged 47 to 81 years old (https://www.ukbiobank.ac.uk/). Data types inclusion criteria for this sub analysis included glucose diagnosed diabetes, principle components analysis (PCA) + Oblimin derived Z-scored anxiety and depression factors from a ‘mental health’ touch-screen questionnaire, a fluid intelligence composite score, AD parental history and APOE4 genotype and normal cognition.

Task based fMRI

Task based fMRI can detect fluctuations in brain blood flow during tasks, such as cognition or tasks that induce emotion. Signal is detected due to the neural activation induced by these tasks. By use of blood-oxygen-level dependent contact (BOLD), fMRI research studies often couple specific emotional or cognitive processes with underlying neural function. The task used during fMRI involved matching shapes and emotionally negative faces. This task was chosen because it can engage a range of neural systems like the fusiform gyrus (i.e. face perception) and amygdala (i.e. emotional) areas. Contrary to tasked based fMRI, resting state fMRI pinpoints regions of the brain on the premises of common variances in activity over time in the absence of an explicit task. The times points at which fMRI data was collected relative to biomarkers can be seen in Table 4-1.

Statistics

Using linear regression, main effects of age, AD parental history, APOE4 status, and diabetes were tested, as well as separate 2- and 3-way interactions of age, diabetes, and either
APOE4 status or AD parental history at family-wise Alpha of .05. Sex interaction effects were also explored. Data types included fasting glucose, Insulin like growth factor 1 (IGF-1), AD parental history, APOE4 status and measures for depression and anxiety.

RESULTS

We examined fluid intelligence in UK Biobank because normal aging most adversely affects dynamic processing of information versus crystallized factual knowledge\textsuperscript{56-58}. We found associations between genetic AD risk and glucose levels. For main effects and interactions, there was surprisingly no significant effect of age or other factors. Two 3-way interactions, for AD family history or APOE4 x Age x Glucose revealed that, for example, adults with no AD parental history showed similar cognitive decline over 6 years regardless of having no diabetes or diabetes (Figure 4-1). By contrast, adults with parental family history showed markedly better fluid intelligence over time (p<.001) in middle-age, whereas similar adults who were above 65 years of age had worse declines in fluid intelligence (p<.01) (Figure 4-1). These results suggest that there may be a “compensation-collapse” facet of glucose regulation in people who are genetically prone to developing AD.

For affect, each year of age corresponded to lower depression (p<.001) and anxiety (p<.05) Z-scores of 0.02SD and 0.002SD. This reduction in negative affect has been replicated in other studies and corresponds to an increased focus on positive affect. Type 2 diabetes was linked to a 0.2SD higher depression score (p<.001), reflecting an abnormal path of emotion regulation, but not to anxiety scores. Regarding depression, an Age x Diabetes (p<.001) association showed that adults with diabetes relative to no diabetes had higher depression scores in middle aged (+0.44SD) and the aged (+0.17SD). For anxiety, Figure 4-2 illustrates an APOE4 x Diabetes x Age interaction (p<.001). Non-APOE4s (Figure 4-2) with
or without diabetes showed less anxiety in aged versus middle aged, which is typical in most normal aging adults\textsuperscript{59}. APOE4s without diabetes (Figure 4-2, left panel) had higher anxiety in midlife versus non-APOE4s but still showed less anxiety in late-life. APOE4s with diabetes (Figure 4-2, right panel) had less anxiety in midlife but a moderate increase in late-life. AD parental family history had a similar interaction pattern (p<.05). These results suggest that adults with preclinical AD (an APOE4 carrier) and diabetes have a compensation-exhaustion aging trajectory, showing less negative affect in midlife, but then late-life dysfunction similar to disturbances in MCI and AD\textsuperscript{24–26}.

For preliminary resting state fMRI data, adults with physician-diagnosed diabetes, APOE4 status, or AD parental history were 6.5\%, 27\%, and 10\% of sample. Cross-sectional mean network strength was derived in AD and affect related networks\textsuperscript{60–68} as described\textsuperscript{69} (Figure 4-3). For main effects, diabetes was linked to 3.7\% less activity in central executive network (p<.05). For interactions, 3-way Parental History or APOE4 Status x Diabetes x Age effects were seen in all networks (p<.05 to p<.01). For example, in default mode network (DMN), among adults with no AD parental history (Figure 4-3, left graph), having diabetes versus no diabetes was linked to less DMN strength in middle and late-life. By contrast, in adults with AD parental history (Figure 4-3, right graph), diabetes in middle versus late-life was related to 1.5SD more versus. 2SD less DMN strength.

Fearful or angry faces versus shapes trials induced activity in areas involved in threat detection, affect salience, and “top-down” affect. (Figure 4-4A). For the main effect, Figure 4-4B shows that participants with diabetes (left “blue” curve) had 1.49SD less global activation (p<.01) in all areas compared to the controls (right “red” curve). Lower global fMRI task activity was related to higher depression (p<.05) but not anxiety factor score. A
3-way interaction for APOE4*Age*IGF1 (p= <.05) revealed that for example, adults with diabetes with a APOE4 genotype had a significantly lower mean in the fMRI faces shapes contrast than the group without APOE4 (\(\bar{x}\) non-APOE4=1.55, \(\bar{x}\) APOE4=1.49; p<.05), reflecting lower global activity. This trend can be seen Figure 4-4 (right graph).

**DISCUSSION**

Diabetes and task fMRI studies have focused on attention or working memory, since IR and diabetes profoundly impact executive function\(^{70}\). Most other paradigms focus on food salience in obese participants. Little work has been done on emotion regulation, reactivity, or negative affect. A study that examined obese adults during an angry/fearful face versus shapes task had less activity in hippocampus, amygdala, and inferior temporal cortex\(^{71}\). Our study showed less activity in the amygdala during this task for participants with diabetes. While other studies have examined IR\(^{72}\) and fasting versus elevated blood glucose\(^{73}\) on fMRI affect tasks, these studies had sample sizes N<20, liberal thresholds, and unclear designs.

Diabetes hyperactivity compared to hypoactivity in middle compared to aged individuals may track preclinical AD progression, as APOE4 carrier in some studies shows higher versus lower default mode activity in middle-aged compared to aged individuals\(^{74,75}\). Critically, participants with major depression also show less neural activity in default mode and other networks that correlates with depressive symptoms\(^{76}\). Diabetes and IR are associated with less strength within and between neural networks that are affected by AD, ones that mediate affect salience, emotional regulation via reappraisal, or self-referential processing. These associations involve the default mode network\(^{78}\), medial frontal cortex\(^{79}\), dorsal and ventral attention networks\(^{80}\), and the central executive function network\(^{81}\). Higher IR is also correlated with less network strength\(^{81}\). Intranasal insulin\(^{82}\) or “healthy lifestyle”
changes for diabetes participants increases network strength within or between several networks, though APOE4 status may change these effects. Interestingly, a research study indicated depressed participants with diabetes versus without diabetes have less network strength between the amygdala and critical emotion regulation areas, like ventral prefrontal cortex and cingulate gyrus.

To our knowledge, no task fMRI studies have tested if diabetes and IR are linked to activity during emotion induction or regulation tasks in preclinical AD, MCI, and AD. Since APOE4 and AD parental history interact with diabetes and IR to increase AD risk and may lead to neuropsychiatric disturbances in late-life, similar interactions may occur for affect task fMRI. This is especially important because task activity may be a very early AD marker in the absence of amyloid deposition.

More research is needed on how diabetes, fasting glucose, IR are related to early AD imaging markers in preclinical AD, MCI, and AD in comparison to normal aging. The hope of this preliminary data is to provide information to inform AD clinical trials with secondary outcomes related to MR imaging and to examine how diabetes may affect the brain and changes in neuropsychiatric disturbances over time.

Acknowledgements

This study was funded in part by the College of Human Sciences at Iowa State University, a Big Data Brain Initiative grant through the Iowa State University Office of Vice President for Research, NIH grant AG047282, and the Alzheimer's Association Research Grant to Promote Diversity grant AARGD-17-529552. The data used in the preparation of this article were obtained from the UK biobank database (https://www.ukbiobank.ac.uk/).
Author contributions: T.W., A.A.W., B.K., C.P, Q.C, and K.M. researched the data and analyzed the data. T.W. and A.A.W. wrote the manuscript. A.A.W. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References


Tables and Figures

Table 4-1: Time table of when variables of interest were collected.

<table>
<thead>
<tr>
<th>Study Timeline</th>
<th>2008</th>
<th>2012</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Year</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Touch Screen Questionnaire</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>fMRI</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>
Figure 4-1: Fluid Intelligence, AD risk, and Glucose. Error bars 95% confidence interval shown. Adults with no AD parental history (left graph) showed similar cognitive decline over 6 years regardless of having no diabetes or diabetes. By contrast, adults with parental family history showed (right graph) showed better fluid intelligence over time (p<0.001) in middle-age, whereas similar adults who were above 65 years of age had worse declines in fluid intelligence (p<0.01).
Figure 4-2: Diabetes, APOE4, and Anxiety UK Biobank. For anxiety, there was an APOE4 x Diabetes x Age interaction (p<0.001). Non-APOE4s (tan color) with or without diabetes showed less anxiety in aged versus middle aged. APOE4s without diabetes (left panel graph) had higher anxiety in midlife versus non-APOE4s but still showed less anxiety in late-life. APOE4s with diabetes (right graph) had less anxiety in midlife but a moderate increase in late-life. AD parental family history had a similar interaction pattern (p<0.05).
Figure 4-3: Diabetes and Neural Networks UK Biobank. Networks are displayed radiologically on a T2* template in MNI space. *, **, *** = p<.05, p<.0001. Values are M±SD. METHODS. EPI data was PCA and group ICA decomposed, and 21 orthogonal neural networks derived and back reconstructed for participants. Displayed are: 1) default mode network (DMN); 2) an affect salience network in cingulate gyrus, dorsal thalamus, and orbital prefrontal areas; 3) an affect regulation network in anterior insula, amygdala, nucleus accumbens, and ventromedial prefrontal areas; and 4) central executive function network. Covariates were sex, education, APOE4 status, WMH volume, and arterial stiffness.
Figure 4-4: The graph shows face > shape contrast, AD risk, and IGF-1. BOLD signal was derived from faces > shapes trials. The brain image (A) shows the activation of the middle frontal gyri, insula and amygdala during this task. Image (B) show those with diabetes had less activation in the amygdala. For the main effect, Figure 4-4B shows that participants with diabetes (left “blue” curve) had 1.49SD less global activation (p<0.01) in all areas compared to the controls (right “red” curve). Lower global fMRI task activity was related to higher depression (p<0.05) but not anxiety factor score. A 3-way interaction for APOE4*Age*IGF1 (p= <0.05) revealed that for example, adults with diabetes with a APOE4 genotype had a significantly lower mean in the fMRI faces shapes contrast than the group without APOE4 (x̅ non-APOE4=1.55, x̅ APOE4=1.49; p<0.05), reflecting lower global activity. This trend can be seen Figure 4-4 (top graph, right graph).
CHAPTER 5. STRATEGIES FOR IMPROVING DASH DIET COMPLIANCE TO REDUCE THE RISK OF HEART DISEASE IN HYPERTENSIVE INDIVIDUALS

Modified from a paper to be submitted to Journal of Nutrition Education and Behavior.

Tovah Wolf\textsuperscript{1}, Maren Wolff\textsuperscript{1}, Christine Komjathy\textsuperscript{1}, Angelique Brellenthin\textsuperscript{2}, Duck-chul Lee\textsuperscript{2}, Ruth Litchfield and Lorraine Lanningham-Foster\textsuperscript{1}

\textsuperscript{1}\textit{Department of Food Science and Human Nutrition, Iowa State University, Ames, IA, United States.} \textsuperscript{2}\textit{Department of Kinesiology, Iowa State University, Ames, IA, United States.}

Abstract

Objective

Compare DASH diet compliance by sex, age, race and ethnicity among participants receiving a baseline 30- minute education sessions on DASH eating followed by one-on-one nutrition counseling with a Registered Dietitian at 3, 6, and 9 months during the 12-month study. Several studies have shown the cardiovascular health benefits of the Dietary Approaches to Stop Hypertension (DASH). However, individuals with hypertension are less likely to follow DASH than individuals without hypertension.

Methods

Researchers were blinded to the groups in this phase 3 randomized controlled trial (RCT) of exercise. Participants undergo exercise training three times per week for one year consisting of aerobic exercise, resistance exercise, a combination of both, or delayed exercise (control). Three 24-hour dietary recalls per month were collected from participants using ASA24\textsuperscript{TM}. Individuals who completed at least 2 diet recalls in a month were included in the analyses for this chapter. Participants had elevated or stage I hypertension, with a mean age of 53 years old, an average BMI of 32 kg/m2, and not on blood pressure medication. At the start of the study, 71\% of these individuals completed 80\% or more of their diet recalls within 3 months. For the individuals examined in this study, by month 12, 69.5\% completed
80% or more of their recalls. DASH diet compliance was assessed by the DASH score.

ANOVA and Least Square Means (LSM) were used to compare scores between sex, age and ethnic groups. A significance level of .05 was used for statistical tests.

**Results**

At month 2, Men’s and Women’s DASH score was not significantly different (\(\bar{x}\) females=2.11, \(\bar{x}\) males=2.31; p=0.1709). Month 2 was examined due to month 1 missing many recalls due to it being the recruitment period of the study. At month 9, Men’s DASH score was higher than women’s (\(\bar{x}\) females=2.4, \(\bar{x}\) males= 3.1; p=0.04). Women had a significantly higher DASH score at month twelve (\(\bar{x}\) females= 2.38, \(\bar{x}\) males= 2.02; p=0.0296). At month 12, women between the ages of 35-45 and men between the ages of 56-65 years old had a higher DASH score than all other age groups in their gender category. Hispanics had a significantly higher DASH score at month 9 than those who identified as not Hispanic or Latino (\(\bar{x}\) DASH score Hispanics=4.3, \(\bar{x}\) not Hispanic or Latino=2.3; p= 0.0079).

**Conclusions**

Men’s DASH score increased significantly during the first 9 months of the study, women’s DASH score did by the end of the study. One’s ethnicity may also influence adherence to DASH.

**Acronyms:** DASH, Dietary approaches to stop hypertension; \(\bar{x}\)= mean; HTN, Hypertension; yr=year; %=%percent; \(\Delta\)= change.

**Introduction**

Heart disease continues to kill more Americans each year than any other condition. Hypertension, which has been associated with diets high in sodium, is a major risk factor for heart disease and stroke. One out of every two American adults has hypertension\(^1\), and it is
estimated that one billion people have the disease globally\(^2\). Dietary approaches to stop hypertension, or more commonly known as DASH, is a dietary approach that can prevent or lower high blood pressure\(^3\). It promotes the consumption of vegetables, fruit, nuts, seeds, beans, fat-free or low-fat dairy, whole grains, fish and poultry. The goal of DASH eating is to increase the intake of potassium, magnesium, calcium, protein and fiber. These nutrients have all been shown to aid in blood pressure reduction. When the DASH diet is implemented, it results in lowered intake of sodium, red meat, sweets and added sugar, sugar-sweetened beverages and fats. Years of studies have demonstrated the health benefits of DASH eating, but there has been low adherence. In fact, one review study revealed that individuals with hypertension were less likely to follow DASH than individuals who did not have hypertension\(^4\). Currently there are different approaches to evaluate DASH compliance\(^5\), including feeding trials, assessment of DASH dietary patterns, urinary analysis and compliance measured by a DASH score. In 1999 the linear index model was established for assessing nutrient intake\(^6\) and Mellen and colleagues established a DASH score based on this method\(^7\). The DASH score is used in the present study as an indicator of compliance due its potential adaptability in a healthcare setting.

In this study, we investigated DASH diet compliance by sex, age, race and ethnicity among participants receiving a baseline 30-minute education sessions on DASH eating followed by one-on-one nutrition counseling with a Registered Dietitian at 3, 6, and 9 months during the 12-month study. We also examine self-confidence for their DASH set goal during the sessions with the dietitians and if it had a relationship with the DASH score. Diet compliance was assessed using the DASH score. This study builds on our interdisciplinary team’s research, funded by the NIH (R01HL133069), evaluating a supervised exercise
training program implemented 3 times per week for one year consisting of 1) aerobic exercise 2) resistance exercise 3) a combination of both, or 4) delayed exercise (which they will receive 1 year of exercise after the study). In addition, all cohorts receive individual nutrition counseling on the DASH diet by a Registered Dietitian. We are interested in this population because exercise and healthy diet are common lifestyle modifications that most people try to improve simultaneously. In addition, hypertensive populations historically have shown to experience cardiovascular health benefits when adhering to the DASH diet.

**Methods**

**Participants**

The study’s total population is 400 inactive (<150 min/week of exercise over the past 3 months) and overweight/obese (BMI 25-40 kg/m²) adults aged 35-70 years with elevated or stage 1 hypertension (SBP/DBP of 120-139/80-89 mmHg). This sub-analysis includes 270 participants. To be included in a graph or analyses, the participants had to have completed at least two out of the three recalls in a given month. ASA24™ was used to collect information of the recollection of foods consumed during the previous 24 hours.

**Determination of pre-hypertension, hypertension stage I and weight status**

During the initial education/screening sessions, neither the systolic or diastolic blood pressure readings could exceed 140/90 mmHG on 2 out of 4 measurements. Additional exclusion criteria included pregnancy, acute/chronic conditions not medically managed (e.g., unstable coronary heart disease or heart failure, acute myocarditis, uncontrolled arrhythmias), taking weight reduction medications or medications known to affect weight, or other medical conditions that are considered life-threatening or can interfere with or be aggravated by the exercise training.
Participants Height and Weight

Weight and height were measured twice and averaged (shoes removed, limited clothing) using a calibrated digital scale and stadiometer (SECA 769, Hamburg, Germany) at 5 time points (baseline, 3, 6, 9 and 12 months).

Participants Dietary Intake and DASH Diet Compliance

We sent three, 24-hour diet recalls via email or text prompts (Appendix J) on random dates asking participants at baseline and each month of the 12-month study using the Automated Self-Administered 24-hour recall (ASA24™). ASA24 is an automated Self-Administered 24-hour recall (ASA24™, NIH Bethesda, MD) that is based on the USDA Automated Multiple-Pass Method (AMPM), which accurately estimates mean total energy and protein intakes relative to recovery biomarkers. The ASA24™ is an online self-administered research tool which allows for the collection of diet information from individuals.

The resulting data files include foods, food groups, and nutrients. The DASH score was assessed using diet information collected from the ASA24™. The nutrition data from these recalls were downloaded, and the DASH scoring was applied (see Table 5-1) to assess if DASH diet compliance was improved. We used this method rather than diet records due to research supporting that weighing and recording intake of foods over several days can be a nuisance, time consuming and is also associated with poor compliance rates and/or a change of diet during that time period.

To calculate the DASH score, nine nutrients obtained from three 24-hour diet recalls in ASA24™ which include sodium, potassium, magnesium, calcium, protein, fiber, total fat,
saturated fat and cholesterol were analyzed. Participants who did not have at least 2 out of 3 recalls completed in the month were not included in the analysis because an average could not be created. The DASH scores can range from 0 to 9 and were obtained by adding the nine nutrient scores together (Table 5-1). If a participant obtains a score of 1 for a particular nutrient, they had to meet the target goal for that particular nutrient. Meeting the intermediate DASH target goal is .5 points, and not meeting the DASH target goal is 0 points. This scoring system has been used in other research studies. A time table for the study is shown in Table 5-2.

**Self-Efficacy Related to DASH eating goal**

Participants rated their self-confidence for their DASH eating goal on a self-report instrument using a scale of 1 to 10 on how confident they are about achieving that goal (Appendix E). This DASH goal was set when participants met with a Registered Dietitian for one-on-one for nutrition counseling at 3, 6 and 9 months. They also had the option whether they wanted no follow up, an email follow-up every 4 or 6 weeks (Appendix L) or a phone follow up every 4 or 6 weeks regarding their goal. An email was sent to schedule this appointment (Appendix M). This goal was emailed to them after the session (Appendix K). The 24-hour diet recall information was examined to see if there was a relationship between self-efficacy and DASH diet score.

**Physical Activity**

In this study, the training computer program is Technogym Wellness System (Technogym, Cesena, Italy) implemented 3 times per week in hypertensive cohorts for one year consisting of 1) aerobic exercise 2) resistance exercise 3) a combination of both, or 4)
delayed exercise (which they will receive 1 year of exercise after the study). This system requires the participants to input an exercise key (similar to a jump drive) into the machine, which then guides the participant to the pace and repetitions. The system collects and records data on exercise type, frequency, duration, and intensity in each session. In this study, each participant wears a pedometer (Omron HJ-321, Omron Healthcare, Inc. Lake Forest Illinois), which can be clipped anywhere on their body or in their pocket, daily to ensure they were remaining within the inactive physical activity category when they were not at the gym. Only inactive individuals were recruited for this study.

**Data Collection Procedures**

The CardioRACE protocol was approved by ISUs institutional review board from Iowa State University (IRB ID 17-101) (Appendix A). At baseline all participants receive a 30-minute DASH education (Appendix B) and 15 minutes of instruction on how to use ASA24™ (Appendix C). Handouts were given to aid in use of learning ASA24™ (Appendix G & Appendix H). At 3, 6 and 9 months each participant receives DASH nutrition counseling. Two RDN’s conduct these sessions by following a script that is based on motivational interviewing (MI) and brief action planning (BAP) (Appendix D). The primary goal of the one-on-one nutrition DASH eating counseling with a MI/BAP component will be to understand if this counseling approach increases compliance of following the DASH eating plan, which is not in the scope of this report. An optional questionnaire related to participants’ experiences with the nutrition visits was administered at their month 12 assessment (Appendix F). Prior to filling out this form, a Dietitian reviewed with the participant information entered from there ASA24™ diet recalls from baseline to month 12. Note this Dietitian was one that had not seen during the study. Following the study, the
participants have the option to review an overview of the nutrition during the course of the study (Appendix N). The project manager met with participants at the CardioRACE gym to review the consent process, followed by the questionnaire data completion, and collection of demographic data, height, weight and body composition measurements at baseline.

**Delayed Intervention (delayed exercise group) Control Participants**

The same data collection procedures were implemented with delayed intervention control participants. They are recruited and assessed at the same time as the intervention groups. They receive the same one-on-one DASH eating counseling as the exercise intervention groups. The researcher RDNs in the study are blinded to group assignment until the study is completed. As a result, the exercises groups in this study are not revealed.

**Concealment**

Baseline data is blinded to participants and investigators until the intervention is complete. Research staff collecting the outcome measures pre- and post-intervention are blinded to treatment (exercise groups or delayed intervention).

**Data Analysis**

All analyses were conducting using R1.2.1335. Diet compliance was assessed by the DASH score. Individuals who had at least 2 diet recalls in a month were included in the analysis. Least Square Means (LSM) and ANOVA were used to compare DASH scores and self-efficacy (confidence) between sexes, ages, and ethnicities. A significance level of .05 was used for statistical tests. Covariates included age, sex, and BMI at baseline.
Results

DASH Score

At month 2, Men’s and Women’s DASH scores were not significantly different (\( \bar{x} \) females=2.11, \( \bar{x} \) males=2.31; \( p=0.1709 \)). Of those who participated in nutrition visits and had at least 2 diet recalls during that month, at month 9, Men’s DASH score was higher than women’s (\( \bar{x} \) females=2.4, \( \bar{x} \) males= 3.1; \( p=0.04 \)). Men also had a significantly higher DASH score change between 1 and 9 months when compared to women (\( \% \Delta \bar{x} \) females = -1.31\%, \( \% \Delta \bar{x} \) males= 3.42\%; \( p<0.0001 \); see Figure 5-1). The 35-45 year old men (\( \bar{x} \) DASH score=2.67) had a significantly higher 12 month DASH score than the 46-55 year old men (\( \bar{x} \) DASH score=1.63; \( p<0.0001 \)) and the 66-69 year olds (\( \bar{x} \) DASH score= 1.86; \( p=0.0064 \)). The 46-55 year olds had a significantly lower 12 month DASH score than the 56-65 yr olds (\( p=0.001 \)) and the 56-65 yr old men (\( \bar{x} \) DASH score= 2.50) had a significantly higher 12 month DASH score than the 66-69 yr olds (\( p=0.0493 \)) male participants (see Figure 5-2).

Women had a significantly higher DASH score at month 12 (\( \bar{x} \) females= 2.38, \( \bar{x} \) males= 2.02; \( p= 0.0296 \); see Figure 5-4), but not significantly higher average calorie intake during the study (\( \bar{x} \) males kcals=2220, \( \bar{x} \) females kcals=1820). In addition, DASH score at month 12 (see Figure 5-3) for the women between the ages of 35-45 (\( \bar{x} \) DASH score=2.88), was significantly higher than the 46-55 yr old women (\( \bar{x} \) DASH score= 1.76; \( p<.0001 \)), the 56-65 yr old women (\( \bar{x} \) DASH score= 2.10; \( p=0.0028 \)), and the 66-69 yr old women(\( \bar{x} \) DASH score= 2.31; \( p=0.0238 \)).

Significant differences were not found based on ethnicity and race of those who attended nutrition visits. However, looking at completed diet recalls across the entire study, Hispanics had a significantly higher DASH score at month 9 than those who identified as not Hispanic or Latino (\( \bar{x} \) DASH score Hispanics=4.3, \( \bar{x} \) not Hispanic or Latino=2.3; \( p= 0.0079 \);
see Figure 5-5), though this is not seen at month 12 ($\bar{x}$ DASH score Hispanics=1.73, $\bar{x}$ not Hispanic or Latino=2.07; p=0.9209). The DASH score over the course of the study by age group, sex, ethnicity and race can be seen in Figure 5-6. Though not significantly different, Asians had a higher trending DASH score over the course of the study than the other ethnic groups (see in Figure 5-6).

**Self-efficacy and Goal Setting**

No significant differences were found between gender, age, race or ethnic groups relative to setting DASH diet goals to test if those who set DASH diet goals were more likely to not to have a higher DASH score. There were also no significant differences found between gender, age, race or ethnic groups on a scale of 1 to 10 in their confidence of achieving that goal. These results and other non-significant results are summarized in Table 5-5.

**Month 12 Questionnaire**

A questionnaire related to participants’ experiences with the nutrition visits was given (Appendix G). Preliminary results show that the majority of participants found the nutrition information they received, goal setting, goal follow up via emails or calls, and working with a Registered Dietitian helpful (see Table 5-4).

**Discussion**

Males consumed more total calories than females and, as a result, they were likely to have better DASH scores up to month 9. Kim et al. came to this conclusion as well$^4$. With the DASH score we used, five out of the nine nutrients achieved by consuming above a certain
target (Table 5-1; protein, calcium, magnesium, potassium and fiber). Therefore, the more food one consumes, the more likely they are to achieve the target amount of these nutrients. However, in our study women showed a significantly higher DASH score at month 12. If the study were to go on, the researchers suspect this fluctuation on DASH score between genders would continue to be observed. It should be noted as well, additional analysis revealed when nutrients were matched to calorie levels between males and females by obtaining the ratio of nutrients to calories, significant differences between the ratios of males and females were not found, suggesting there may not be a meaningful differences in DASH score between sexes when taking into account calorie intake.

The researchers are not surprised the Hispanics showed a higher DASH score and that the Asians showed a trend of a higher DASH score throughout the study. The Dietitian’s on the study noted that many of the ethnic minorities in the study are not assimilated to the western diet yet. Many studies have shown the numbers of years since immigration is associated with an increase in BMI\textsuperscript{20,21,22}. These studies highlight and suggest that immigrants tend to adapt to an “obesogenic” lifestyle over time in the USA. An obesogenic lifestyle is characterized by diet and physical activity patterns that promote as positive energy balance and hence weight gain. Taking these results into account, it would be worthwhile to put efforts into programming for ethnic minorities in tactics on acculturation prevention techniques to decrease the promotion of a sedentary and obesogenic lifestyle.

Our long-term goal is to develop effective DASH intervention strategies that increase diet compliance in individuals who are at high risk of cardiovascular disease (CVD). This study set forth to look at if there are differences between sex, age, ethnicity and race due to seeking better understanding if counseling methods and education methods need to be
tailored towards these groups. Currently, many studies with USA adults are conducted with one gender (not both), so this report has the advantage of examining both males and females DASH score over the course of 1 year. Our results suggest that different efforts may not be tailored at different age groups, since the 35-45 year old women, and the 56-65 years old men had higher DASH scores than other age categories.

Future work at the end of the full study will investigate the impact of DASH nutrition counseling with a motivational interviewing and brief action planning approach for self-management strategies. Motivational interviewing is a counseling method that can be used by psychologists, dietitians, physicians and other health care providers to encourage behavior change, such as improving poor eating habits by increasing fruit and vegetable intake\textsuperscript{23}. Brief action planning can be used to help individuals develop an action plan to increase self-efficacy for disease prevention and management\textsuperscript{24}, and it has also been shown to increase fruit and vegetable consumption\textsuperscript{25}. For our future work, we hypothesize that incorporating motivational interviewing with brief action planning into DASH diet counseling, in addition to exercise, will increase the DASH diet compliance as reflected by the DASH diet score.

Ultimately, this work will enable us to test a multi-component hypertension intervention strategy that is uniquely aimed at hypertensive individuals (who are not on antihypertensive medication) to promote blood pressure reduction and healthy eating-related behaviors before the condition progresses. This study has demonstrated that the intervention has the possibility to improve the health of participants within the context of overall health and well-being, as well as offer a scalable approach to cardiovascular disease prevention and management.
Acknowledgements

This work is directly supported by the NIH (HL133069). The authors would like to thank Katherine Goode, Kellie McClernon and Dr. Sebastien Pouliot for their expertise in statistics and automation of the DASH score with R code. TW would also like give a special thank you to Katherine Goode for her advice on statistical analysis. TW would also like to give a very special thank you to Ellie Schmidt, Nicole Kling, Kate Kokemiller, Jennifer Pilut, Lisa Smith, Yayan Chen, Zoe Sirotiak and the many other undergraduate students who are crucial part to keeping human studies running.

Authors’ Contributions

TW, MMW, and LLF all contributed to the protocol and survey design. TW, AB, CK, ES and MMW collected the data. TW analyzed the data. TW drafted the manuscript. LF edited the manuscript. All authors reviewed the final manuscript.

Author Disclosure Statement

No competing financial interests exist

References


## Tables and Figures

Table 5-1: DASH scoring table to determine DASH Score

<table>
<thead>
<tr>
<th>DASH Nutrient</th>
<th>1 point if hit DASH score target values</th>
<th>.5 points if hit Intermediate target values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium (mg/day)</td>
<td>&lt;2300</td>
<td>2300-2650</td>
</tr>
<tr>
<td>Cholesterol (mg/day)</td>
<td>&lt;149.1</td>
<td>149.1-224.7</td>
</tr>
<tr>
<td>Saturated Fat (% of kcal/day)</td>
<td>&lt;6.0</td>
<td>6 - 11 %</td>
</tr>
<tr>
<td>Total Fat (% of kcal/day)</td>
<td>&lt;27.0</td>
<td>27 - 32 %</td>
</tr>
<tr>
<td>Protein (% of kcal/day)</td>
<td>&gt;18.0</td>
<td>16.5-18.0 %</td>
</tr>
<tr>
<td>Calcium (mg/day)</td>
<td>&gt;1240</td>
<td>842.3-1240.0</td>
</tr>
<tr>
<td>Magnesium (mg/day)</td>
<td>&gt;496.7</td>
<td>330.3-496.5</td>
</tr>
<tr>
<td>Potassium (mg/day)</td>
<td>&gt;4673.3</td>
<td>3198.3-4673.3</td>
</tr>
<tr>
<td>Fiber (g/day)</td>
<td>&gt;30</td>
<td>19.5-30</td>
</tr>
</tbody>
</table>

Table 5-2: Time table of the study timeline

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>X₀ (pre)</td>
<td>X₆</td>
<td>X₁₂</td>
<td>X₁₈</td>
<td>X₂₄ (post)</td>
</tr>
<tr>
<td>Wait list</td>
<td>X₀</td>
<td>X₆</td>
<td>X₁₂</td>
<td>X₁₈</td>
<td>X₂₄ (pre)</td>
</tr>
</tbody>
</table>

X=Data collection point (months 0, 6, 12, 18, 24). For the immediate intervention group, intervention takes place between O₀ and O₁₂ and for the delayed exercise group intervention takes place between O₁₂ and O₂₄. One-on-one nutrition DASH counseling takes place at 3, 6, and 9 months.
Table 5-3: Demographics of participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Females (n)</th>
<th>Males (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>148</td>
<td>122</td>
</tr>
<tr>
<td>Racial or ethnic minority, n</td>
<td>22</td>
<td>31</td>
</tr>
<tr>
<td>Age (average)</td>
<td>50</td>
<td>49</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>32</td>
<td>30.3</td>
</tr>
<tr>
<td>Past Smoker (n)</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Junior High</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>High School</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Associate/Technical Degree</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>Bachelor’s Degree</td>
<td>57</td>
<td>42</td>
</tr>
<tr>
<td>Graduate School</td>
<td>52</td>
<td>61</td>
</tr>
<tr>
<td>Income</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$12,000</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>$12,000-24,999</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>$25,000-49,999</td>
<td>16</td>
<td>8</td>
</tr>
<tr>
<td>$50,000-74,999</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>$75,000-100,000</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>&gt;$100,000</td>
<td>66</td>
<td>64</td>
</tr>
</tbody>
</table>
Table 5-4: Twelve month questionnaire participant responses (total respondents n=17)

<table>
<thead>
<tr>
<th>Question</th>
<th>Strongly Agree (n)</th>
<th>Agree (n)</th>
<th>Neutral (n)</th>
<th>Disagree (n)</th>
<th>Strongly Disagree (n)</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1. I found the levels of Sodium, Magnesium, Potassium, Calcium, Protein and Fiber provided at the top of the nutrition forms helpful</td>
<td>2</td>
<td>9</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Q2. I found the nutrition goal setting helpful (back of nutrition forms during the nutrition visits)</td>
<td>0</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Q3. I found the nutrition follow up emails or phone calls every 4-6 weeks helpful</td>
<td>0</td>
<td>9</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Q4. I found the food lists sent by the Dietitians via email (if requested) helpful</td>
<td>0</td>
<td>5</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>Q5. I read the nutrition information in newsletters and found it helpful</td>
<td>0</td>
<td>9</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Q6. I found working with a Registered Dietitian helpful</td>
<td>4</td>
<td>9</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 5-5: Model estimate marginal means (EMM) and SE of DASH score indices at month 12. The parameters listed in the table are also non-significant at baseline, month 3, 6, 9 and 12 and the changes between baseline and month 3, 6, 9 and 12.

<table>
<thead>
<tr>
<th>Parameter tested with DASH score indices at month 12 (contrasts between groups shown)</th>
<th>Estimate ± SE</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI Categories</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>normal weight : obese class 1</td>
<td>-0.277±0.581</td>
<td>0.989</td>
</tr>
<tr>
<td>normal weight : obese class 2</td>
<td>-0.034±0.599</td>
<td>1.000</td>
</tr>
<tr>
<td>normal weight : obese class 3</td>
<td>0.158±0.720</td>
<td>1.000</td>
</tr>
<tr>
<td>normal weight : overweight</td>
<td>-0.962±0.545</td>
<td>0.400</td>
</tr>
<tr>
<td>obese class 1 : obese class 2</td>
<td>0.244±0.371</td>
<td>0.965</td>
</tr>
<tr>
<td>obese class 1 : obese class 3</td>
<td>0.436±0.529</td>
<td>0.993</td>
</tr>
<tr>
<td>obese class 1 : overweight</td>
<td>-0.684±0.311</td>
<td>0.188</td>
</tr>
<tr>
<td>obese class 2 : obese class 3</td>
<td>0.192±0.554</td>
<td>0.997</td>
</tr>
<tr>
<td>obese class 2 : overweight</td>
<td>-0.928±0.351</td>
<td>0.070</td>
</tr>
<tr>
<td>obese class 3 : overweight</td>
<td>-1.120±0.523</td>
<td>0.210</td>
</tr>
<tr>
<td><strong>Ethnicity Category</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino : Not Hispanic or Latino</td>
<td>-0.498±0.898</td>
<td>0.844</td>
</tr>
<tr>
<td><strong>Race Categories</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian : Black</td>
<td>0.396±1.345</td>
<td>0.953</td>
</tr>
<tr>
<td>Asian : White</td>
<td>0.623±0.446</td>
<td>0.346</td>
</tr>
<tr>
<td>Black : White</td>
<td>0.226±1.272</td>
<td>0.9827</td>
</tr>
<tr>
<td><strong>Goal set confidence scale 1 to 10 with sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females: Men</td>
<td>0.029±0.181</td>
<td>0.873</td>
</tr>
<tr>
<td><strong>Goal set confidence scale 1 to 10 with ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino : Not Hispanic or Latino</td>
<td>-0.753±0.866</td>
<td>0.661</td>
</tr>
<tr>
<td>Not Hispanic Latino : Prefer not to respond</td>
<td>0.753±0.866</td>
<td>0.661</td>
</tr>
<tr>
<td><strong>Goal set confidence scale 1 to 10 with race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian : White</td>
<td>0.533±0.289</td>
<td>0.158</td>
</tr>
<tr>
<td>Black : White</td>
<td>0.533±0.289</td>
<td>0.158</td>
</tr>
<tr>
<td><strong>Action plan</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No action plan or goal: Yes Action plan and goal</td>
<td>0.050±0.187</td>
<td>0.7886</td>
</tr>
</tbody>
</table>
Figure 5-1: Percent Change in DASH score between 1 and 9 months (n=94: 40 females, 45 males; p<0.000). The mean percent change for females was 3.42%.
Figure 5-2: DASH score at month 12 for the men (n=106). The 35-45 year old men had a significantly higher 12 month DASH score than the 46-55 yr old men (p<.0001) and the 66-69 year olds (p=0.0064). The 46-55 yr olds had a significantly lower 12 month DASH score than the 56-65 yr olds (p=0.001) and the 56-65 yr old men had a significantly higher 12 month DASH score than the 66-69 yr olds (p=0.0493) male participants. The mean scores were the following: $\bar{x}$ 35-45 yr old males=2.67, $\bar{x}$ 46-55 yr old males=1.63, $\bar{x}$ 56-65 yr old males=2.50; $\bar{x}$ 66-69 yr old males=1.86.
Figure 5-3: DASH score at month 12 for the women (n=128). For women between the ages of 35-45 was significantly higher than the 46-55 yr old women (p = <.0001), the 56-65 yr old women (p=0.0028), and the 66-69 yr old females (p=0.0238). The mean scores were the following: $\bar{x}$ 35-45 yr old females= 2.88, $\bar{x}$ 46-55 yr old 1.76, 56-65 yr old $\bar{x}$= 2.10; 66-69 yr old $\bar{x}$=2.31.
Figure 5-4: Women had a higher significantly higher DASH score at month 12 (n=236: 95 females, 108 males; p= 0.0296). The mean scores were the following: \( \bar{x} \) females= 2.38, \( \bar{x} \) males= 2.02.
Figure 5-5: Hispanics had a significantly higher DASH score at month 9 than those who identified as not Hispanic or Latino (n=3, Hispanic/Latino: n=132, not Hispanic/Latino; p=0.0079). The mean scores were the following: $\bar{x}$ DASH score Hispanics=4.3, $\bar{x}$ not Hispanic or Latino=2.3.
Figure 5-6: An overview of the DASH score over the course of the study (12 months) by sex, age groups, ethnicity and race.
CHAPTER 6. GENERAL CONCLUSIONS

Healthy eating and its role in disease prevention is pivotal to disease prevention and treatment. This dissertation and a large body of literature supports this statement. Improving diet quality can impact blood pressure and insulin resistance. Over time, hypertension and insulin resistance can lead to heart disease and potentially death if diet, physical activity and medical treatment cannot improve the condition.

Chapter 3 suggests that dysmetabolism is associated with increased emotional reactivity, predisposition toward negative affect, and specific cognitive deficits; and chapter 4 suggests that the dysmetabolism seen with insulin resistance may impact how one reacts in stressful situations, cognition during tasks, fluid intelligence and potentially increase depressed mood and anxiety as well. Research suggests stress management can lead to improved physical and mental health. Social support is also an important factor in health outcomes and research supports that social isolation can lead to early mortality and morbidity of chronic disease. Clinical studies that monitor IR throughout the treatment of mood disorders would be beneficial to explore as well. If decreased insulin resistance could manipulate emotional regulation to lead to more positive affect, health goals may become more easily obtainable.

Chapter 5 suggests that one’s ethnicity, age and gender my effect their adherence to DASH eating. Our results show Hispanics had a higher DASH score, and that the Asians DASH score also trended higher than other race groups. This suggests the possible explanation that these individuals are not fully assimilated to the western diet yet. Since ethnic minorities are disproportionately affected by chronic disease, intervention efforts to target these populations is crucial, and our study suggests they can obtain a higher DASH score by
adhering to their cultural practices rather than adapting to a westernized eating pattern.

At the conclusion of this study, it will be interesting to see if DASH adherence varies between exercise groups and the control group. As stated before, cardiovascular disease continues to be the leading cause of death in the United States and a major public health concern. As can be concluded from the report above, randomized control studies and epidemiological studies in blood pressure control and insulin resistant treatment need to continue due to the increase in heart disease and insulin resistance prevalence. A “one glove fits all” approach isn’t possible due to genetic, cultural and environmental factors. Implementation of healthy eating can significantly decrease systolic and diastolic blood pressure\textsuperscript{6} by highlighting the combination of nutrients and consuming foods in their whole form that can have an impact on blood pressure. This eating pattern has also shown to decrease insulin resistance\textsuperscript{7–9}. It is interesting to note, that regardless of sodium intake, implementing DASH eating significantly decreased systolic and diastolic blood pressure within 30 days in studies that did not include an exercise intervention\textsuperscript{6}. Therefore, promoting the consumption of a variety of foods can have a meaningful impact on helping combat heart disease.

Combined, general medical cost for diabetes (diabetes.org) and heart disease (cdc.gov) was estimated to be in excess of $527 billion USD. Continued research and collaboration across academic disciplines as well as private, public and government sector involvement and collaboration is paramount to help decrease chronic disease. The obesity epidemic in this country, and globally, is clearly multi-factorial and is a major risk factor for chronic disease. This paper does not encompass all the possible factors that may contribute to the continuing obesity epidemic and in turn, pre-diabetes and heart disease. Not only are
these diseases continuing health concerns, but also they cause a large economic strain on the country. It is essential that treatment programs as well as prevention tactics be explored to decrease disease burden, which in turn will lower health care cost and pave the way for healthier generations.

References


