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Therapeutic potential of a ketogenic diet in the treatment of major depressive disorder

Jordan A. Murrin
James Madison University

Therapeutic Potential of a Ketogenic Diet in the Treatment of Major Depressive Disorder

Jordan A Murrin

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FACULTY COMMITTEE:

Committee Chair: Jeremy Akers, PhD, RDN

Committee Members/Readers:

Laura Dengo, PhD

Aimee Johnson, PhD

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Abstract

Major depressive disorder (MDD) is the second most common mental health condition and a leading cause of disability in the world. It is theorized that MDD develops from a combination of biological, psychological, and social stressors. The condition is typically treated using pharmaceuticals and psychotherapy. However, not all individuals with MDD have access to or choose to use these treatments, or may prefer to incorporate therapeutic lifestyle changes such as exercise, sleep, and healthy eating. Even with treatment, MDD can alter brain structure and function, leading to the development of comorbid mental health and chronic metabolic conditions like obesity, cardiovascular disease, or diabetes. Physiological mechanisms that can be significantly affected by MDD episodes include brain glucose metabolism, brain-derived neurotrophic factor (BDNF) production and activity, and antioxidant function. This paper reviews existing literature to examine these components of the pathophysiology of MDD and outline how treatments could functionally improve the condition. Most research has examined the relationship between nutrition and MDD utilizing traditional interventions, like low-fat diets, but more recent studies have explored alternative nutrition therapies. Animal-models have shown potential for the use of the ketogenic diet as nutrition therapy for MDD by demonstrating improved metabolism of alternative nutrients, increased BDNF activity, and improved antioxidant capacity in the brain. However, to date, there are no studies that examine the effects of a ketogenic diet on a human population with MDD. Future research is warranted to determine whether a ketogenic diet is a safe and reliable medical nutrition therapy for MDD.

Chapter I. Review of Literature

Introduction

MDD, also known as clinical or major depression, has a significant impact on the personal, social, familial, and occupational function of millions of individuals in the US and the rest of the world. According to the World Health Organization (WHO), MDD was the fourth highest cause of disability in the world in 2013 and is on course to be the second highest by the end of 2020.[1] While the lifetime incidence of MDD has been estimated to be between 15 to 20%, there was a 10-year prevalence rise from 6.6% in 2005 to 7.3% in 2015.[1, 2] The incidence of MDD among the general population is characterized by a variety of demographic, socioeconomic, and lifestyle factors. Reported rates of MDD tend to be significantly higher among females,[2, 3] individuals less than 45 years old,[2, 3] non-Hispanic white and Hispanic populations,[2, 3] individuals with annual incomes below $20,000,[2] and individuals with at least some college education.[2] Research has also revealed that MDD is two to three times more common in individuals who already have multimorbidities compared to those with one or no chronic physical conditions.[4] This data indicates a potential risk for a cyclical or synergistic pattern of MDD and chronic disease, due to the inflammatory effect that MDD has on human physiology.

It has been estimated that about 56% of individuals who have depression and at least one other chronic physical condition use antidepressants for treatment, while about 21% use psychotherapy, and about 22% report no treatment.[5] With research indicating that diet, sleep, and exercise all have a significant impact on the development, progression, and management of MDD, there is an opportunity for creating non-

pharmacological interventions that address these factors, especially among those individuals not currently following any treatments for MDD.[6] Additionally, the correlation between poor mental and physical health and the prevalence of individuals with multimorbidities warrants further research into intervention methods that can improve multiple health conditions. To date, most research has utilized dietary interventions that emphasize a higher intake of fruits, vegetables, and whole grains, following a low-fat diet or exchanging high saturated fat foods for those high in unsaturated fats or limiting the consumption of foods that are highly processed or contain high amounts of added sugars.[7] However, with the continued rise in the prevalence of depression, it would be beneficial to continue research into the effects of nontraditional dietary interventions that do not necessarily strictly follow to these typical eating patterns. Therefore, this critical review will describe the pathophysiology of major depressive disorder, including brain nutrient metabolism and oxidative stress, and the relationship between major depression and obesity. Additionally, it will review current research regarding the high-fat, low-carbohydrate ketogenic diet and its mechanistic action on neurophysiological systems that are dysregulated in major depression to outline the therapeutic potential of this type of dietary intervention in the treatment of the condition.

Major Depressive Disorder

To better comprehend the prevalence and effects of MDD, it is necessary to understand its status as a mental health condition and how it is categorized and diagnosed by mental health professionals. MDD is classified as a neuropsychiatric mood disorder and is characterized by a persistently depressed mood or loss of interest in daily

activities. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V), the criteria for a diagnosis of MDD require that[8]:

I. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

   A. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).

   B. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).

   C. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.

   D. Insomnia or hypersomnia nearly every day.

   E. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

   F. Fatigue or loss of energy nearly every day.

   G. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

   H. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

   I. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

II. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

III. The episode is not attributable to the physiological effects of a substance or another medical condition.

IV. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

V. There has never been a manic episode or a hypomanic episode.

A diagnosis of MDD can include either isolated or recurrent episodes, which are typically classified as mild, moderate, or severe. For individuals with MDD, the length and severity of an episode can have a lasting impact on brain structure and function, while recurrent or chronic MDD is likely to lead to the development of other chronic health conditions.

Neuropathology.

MDD is considered to be caused by a combination of various biological, psychological, and social stressors. These factors are likely to alter several components of brain function, in addition to creating an inflammatory state within the body that can affect multiple physiological organ systems. Some of these functions with which MDD interferes in the human body include brain glucose metabolism, regulation of brain-derived neurotrophic factor (BDNF), and antioxidant activity.

***Glucose metabolism*.** Although glucose is typically the main source of energy for the brain, there are significant alterations in the mechanisms of glucose metabolism in populations affected by major depression. Several studies, examining individuals with MDD and concurrent anhedonia, have demonstrated regional glucose hypometabolism and metabolic asymmetry in the left prefrontal cortex, cerebellum, left anterior cingulate, right insular cortex, right claustrum, right anteroventral caudate and putamen, right

middle temporal gyrus, and right superior temporal gyrus.[9-11] These alterations have also been associated with the relative severity and course of the depressive episode, such that individuals with severe depression are likely to have lower global cerebral glucose metabolic rates.[12] It has been shown that successful pharmacological treatment, with specific antidepressants, can increase glucose utilization in the left prefrontal cortex; however, whole frontal glucose metabolism was still significantly lower in both untreated and treated MDD individuals.[10] Holthoff et al. even reported decreases in regional glucose metabolism in remitted MDD patients treated with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[9] These results demonstrate that specific antidepressant treatments may not induce long-term changes in or may have absolute detrimental effects on cerebral glucose metabolism**.** A possible causal link between MDD and decreased cerebral glucose metabolism was found by Kahl et al., showing that elevated DNA methylation of GLUT1 in unremitted MDD patients lowered GLUT1 expression in brain cells, but could be reversed through MDD remission.[13] Although the main alterations to cerebral metabolism are related to glucose metabolic dysfunction, Mocking et al. reported another change in cerebral metabolism, which included elevated fatty acid unsaturation and peroxidation that was negatively associated with higher cortisol levels in individuals with MDD.[14] These findings indicate that glucose uptake from blood vessels into the brain may be compromised in untreated and treated MDD and that another source of energy could potentially improve cerebral metabolic rates for these individuals.

BDNF. Although brain metabolic dysfunction is an important factor in the pathophysiology of depression, there are other noted alterations in brain function, such as

changes to the activity of BDNF. BDNF is the most abundant neurotrophin in the nervous system and is involved in the development and regulation of neuronal systems, neurotransmitter activity, and neuroplasticity.[15, 16] Individuals with MDD have been shown to have significantly lower concentrations of serum BDNF in comparison to healthy controls.[15, 17-22] Lower serum BDNF levels have also been reported during recurrent depressive episodes as compared to first episodes,[17] in individuals with long-term MDD (≥1 year) as compared to short-term MDD (<1 year),[23] and in individuals with MDD as compared to individuals with dysthymia.[20] However, Sözeri-Varma et al. did find a contrasting result by demonstrating that there was no significant difference in serum BDNF levels between individuals in their first and recurrent MDD episodes.[18] In regard to the correlation between MDD treatment and BDNF activity, it has been demonstrated that antidepressants can increase serum BDNF levels in individuals with MDD.[15, 19, 22] While these findings do not indicate that antidepressants only treat MDD by improving BDNF levels, it has been suggested that low BDNF levels play an important role in the pathophysiology of MDD and other affective disorders.[15, 19, 22] Although most data appears to support this hypothesis, there is no evidence for directionality in this relationship, and conflicting data has been shown between serum BDNF levels and the severity of MDD and the presence of psychotic features.[17, 18, 23] The correlation between improvements to reduced BDNF levels and the severity of MDD symptoms warrants additional research, especially regarding treatments and interventions that can improve both of these conditions.

Oxidative Stress. Other prevalent alterations to brain function in MDD can occur through the action of oxidative stress, which can have significant effects on brain

structure and metabolism, and neuronal interaction. Markers of oxidative stress and reduced antioxidant function have been repeatedly noted in individuals with MDD compared to healthy controls.[24-28] The major brain antioxidant glutathione, its complementary enzyme glutathione peroxidase (GPx), and the detoxifying brain isozyme glutathione S-transferase Mu 1 (GST Mu 1) were shown to be significantly lowered in post-mortem brain tissues of individuals with MDD, bipolar disorder, and schizophrenia[24, 29] and the serum of living individuals with MDD.[25, 28] There has been one report of no difference in GPx activity between individuals with MDD and healthy controls.[26] While the previously mentioned enzymes are typically reduced during MDD, there have also been reports of increased activity of the antioxidant enzymes glutathione reductase,[25,29] superoxide dismutase (SOD),[25, 29, 30] and catalase.[26, 30] However in contrast to this, Rybka et al. did find decreased SOD activity in individuals with MDD compared to healthy controls.[28] Additionally, some of these antioxidant activities have not been shown to improve or have even been slightly suppressed with the pharmacological treatment of MDD.[26, 29, 30] These findings illustrate that oxidative stress in psychiatric conditions, including MDD, may be exacerbated by antioxidant dysregulation and dysfunction. Markers of oxidative stress, such as malondialdehyde, 8-OH 2-deoxyguanosine, interleukin-6, tumor necrosis factor-α (TNF-α), F2-isoprostanes, neopterin have also been found in elevated levels in individuals with MDD, and some have been associated with decreased effectiveness of antidepressant treatments.[27-29] Interleukin-6 levels, however, were shown to be decreased by SSRI treatment.[27] The relative ineffectiveness of several antidepressant treatments for improving oxidative

stress in MDD suggests that other therapeutic methods should be examined for the limitation of prooxidant and enhancement of antioxidant systems.

Obesity.

Due to its similar relationship with increased oxidative stress and systemic inflammation, it is important to discuss obesity and how it correlates with MDD. There have been numerous large-scale, cross-sectional epidemiological and observational studies that have examined this relationship, and have demonstrated a positive correlation between obesity and MDD.[31-35] Some studies have reported odds ratios between 1.1 and 2.09 for the risk of developing MDD when the condition is preceded by obesity.[32, 36] Several studies have reported that this association occurs mainly between MDD and severe or class III obesity (body mass index ≥ 40 kg/m^2).[31, 37, 38] Despite this significant correlation, no causal direction of the MDD-obesity relationship has been officially established. However, in their research based on the Alameda County Study, Roberts et al. did report that obesity at baseline was associated with an increased risk of MDD five years later, while the presence of MDD at baseline did not increase the risk of future obesity when controlling for baseline obesity.[32] In this study, the sample was collected from the 1994 and 1999 waves of the Alameda County cohort, including 2,123 individuals who were 50 years or older. This finding suggests a possible causal relationship for the obesity-to-MDD direction, but not vice versa; however, to the knowledge of the researchers, this result has not been obtained in any other research. It has been shown that the presence of overweight or obesity in individuals with MDD is associated with slower clinical and neuroendocrine responses to antidepressant treatment.[39] Additionally, weight loss has been associated with a significant, sustained

reduction in the severity of MDD, with individuals achieving greater weight loss also experiencing the largest reduction in MDD severity.[38] The importance of treating MDD is further emphasized by the correlation between the presence of a current or lifetime MDD diagnosis, in addition to obesity, and an increased risk for the development of other psychiatric disorders, smoking, physical inactivity, alcohol and substance abuse, disordered eating, and other unhealthy behaviors.[31, 33, 36] Although these findings did not determine a specific causal direction in the MDD-obesity relationship, they do suggest the dire need for a multifactorial and comprehensive approach to the treatment of MDD and obesity, beyond pharmaceuticals, especially when the conditions are concurrently present.

Ketogenic Diet

Traditional treatments for MDD may not always be effective in managing physiological consequences of the condition, especially when individuals are experiencing reduced glucose metabolism in the brain, increased levels of oxidative stress, or have multiple comorbidities. A possible alternative or complementary treatment for MDD would be a dietary intervention of the ketogenic diet, which is a high-fat, very low-carbohydrate, adequate-protein eating plan. Typically, it includes an initial reduction of net carbohydrate intake to less than 20 to 50 grams per day with a macronutrient distribution of approximately 0-10% carbohydrate, 60-80% fat, and 10-30% protein as a percent of total energy intake.[40] This severe restriction of carbohydrates lowers glucose availability, thereby decreasing insulin and increasing glucagon concentrations. This creates a metabolic shift in the body away from fat storage to lipolysis and β-oxidation by "imitating" a fasted state.[41] However, in the ketogenic diet, both exogenous and

endogenous protein and fat sources can provide energy, and glucose concentrations can be relatively maintained without carbohydrate intake.[40] The ketogenic diet's alternative nutrient utilization is one of its most important characteristics and may be highly beneficial for the MDD population as they typically have significantly reduced glucose metabolism in the brain. The subsequent sections describe the mechanisms of action related to the ketogenic diet in brain nutrient metabolism, the production of BDNF, regulation of oxidative stress, and weight management that could improve the physiological consequences of MDD.

Neurophysiology.

Ketone Metabolism. As the ketogenic diet restricts carbohydrate intake to a level at which the body is not able to maintain carbohydrate utilization throughout all tissues, it is necessary that the body more effectively use lipids and their metabolites for energy. When energy is mainly provided by fatty acid oxidation in cell mitochondria, large amounts of acetyl-CoA are produced, which are then utilized, primarily in the liver, to synthesize the ketone bodies β-hydroxybutyrate (β-HB), acetoacetate and acetone.[42] Ketosis occurs when the metabolic efficiency of the Krebs, or tricarboxylic acid (TCA) cycle, is reduced and additional acetyl-CoA is converted into ketones.[42] Because the liver does not have succinyl CoA:3- ketoacid CoA transferase, a mitochondrial enzyme that converts acetoacetate to acetoacetyl CoA, ketone bodies are forced into the circulatory system.[43] In ketosis, the levels of the ketone bodies β-HB, acetoacetate, and acetone are increased in the peripheral blood and urine. These ketones are delivered to and serve as a fuel source for numerous extrahepatic tissues, including the brain.[42, 44] This process mainly occurs in metabolic states in which glucose is insufficiently available to

fulfill its normal fuel-based functions. Higher levels of ketosis will proportionally spare glucose from metabolism in the brain and other tissues.[44] This mechanism has great significance in conditions in which glucose availability can be severely limited, as fatty acids are not able to cross the blood-brain barrier to provide energy. This sparing effect of ketones for glucose in cerebral metabolism has been shown in rat models and has demonstrated a coordinated upregulation of energy metabolic genes and an increase in metabolic gene transcripts.[44, 45] To the knowledge of the researchers, no current research has demonstrated these findings in any human population. Despite this lack of research, the ketogenic diet provides an alternative source of energy for the brain, which could benefit individuals with MDD who experience significantly reduced brain glucose metabolism.

BDNF Activity and the Ketogenic Diet. Another aspect of brain function affected by ketone bodies is the concentration and activity of BDNF. Although no studies have demonstrated *in vivo* action of ketones on the expression of BDNF in humans, *in vivo and vitro* animal models have shown ketone-mediated alterations in BDNF gene expression and protein levels.[46-49] At least two models have examined the direct effects of a ketogenic diet on BDNF activity. Genzer et al. showed an increase in the BDNF:proBDNF ratio, whole brain and liver BDNF expression, and BDNF mRNA in a population of C57BL/6 male mice fed an *ad libitum* ketogenic diet.[46] This finding suggests a ketone-induced upregulation of BDNF production, especially in the brain. However, Vizuete et al. demonstrated that BDNF content was decreased in the corpus striatum, but not the hippocampus, in male Wistar rats fed a ketogenic diet.[48] These conflicting results imply that a ketogenic diet may affect BDNF regulation by increasing

total BDNF gene expression and content but reducing regional BDNF synthesis. Another *in vivo* study examined the indirect effects of a ketogenic diet on BDNF activity by using 2-deoxy-D-glucose to induce ketogenesis and ketosis in 3xTgAD mice. In this study, Yao et al. found that 2-deoxy-D-glucose-induced ketosis did not adversely affect mitochondrial function in neurons or mixed glia and stimulated the upregulation of the BDNF and another neurotrophic factor, nerve growth factor (NGF).[49] In an *in vitro* study of exercised male C57BL/6 mice, β-HB was found to increase with exercise and coincided with an increase in BDNF expression and protein levels in cortical neurons.[47] This finding is consistent with the results of the previously discussed *in vivo* studies, as it suggests that β-HB is involved in the *in vivo* regulation of BDNF. Although these studies have only examined animal models, they indicate that there could be benefits of using a ketogenic diet in conditions like MDD, in which BDNF expression or protein levels are lowered.

Oxidative Stress and the Ketogenic Diet. In addition to the previously mentioned metabolic and neurological alterations, the ketogenic diet has been shown to have significant impact on both systemic and brain oxidant-antioxidant systems. The theorized neuroprotective effect of the ketogenic diet is associated with acetoacetate and β-HB and has only been demonstrated in animal models. These studies have shown that a ketogenic diet, via acetoacetate and β-HB action, can protect hippocampal and dopaminergic neurons from glutamate-induced or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) excitotoxicity and can increase glutathione synthesis, Nrf2 protein levels, NAD(P)H dehydrogenase quinone 1 (NQO1) activity.[50-53] The upregulation of these antioxidant substrates could contribute to the ketogenic diet's

protective mechanism against oxidative damage and improvements in mitochondrial redox status. Several animal studies have shown the indirect effects of the ketogenic diet in mediating oxidative stress by decreasing reactive oxygen species (ROS) and free radicals and enhancing mitochondrial antioxidant capacity.[53-55] It is suggested that the reduction in ROS production is achieved by improving mitochondrial uncoupling protein activity, which reduces the membrane potential upon which the ROS production is dependent.[55] The ketogenic diet has also been shown to improve hippocampal mitochondrial antioxidant capacity, specifically by increasing NQO1, SOD1, and GPx expression and decreasing catalase activity in animal models.[56, 57] These animal-based studies demonstrate that the ketogenic diet has the potential for reliable antioxidant, anti-inflammatory, and neuroprotective capabilities in conditions, like MDD and obesity, that are adversely affected by systemic and neural oxidative stress and inflammation. However, more research is needed to determine if the ketogenic diet can reliably improve antioxidant capacity and reduce oxidative damage in humans.

Mood Changes with the Ketogenic Diet.

Several animal studies have demonstrated possible antidepressant or mood-improving properties of the ketogenic diet; however, the exact mechanisms have not been established. Two of these studies appeared to show that a ketogenic diet, mainly through the action of β-HB, reduced "behavioral despair" in stressor-exposed male Wistar rats and depressive-like behaviors in stressor-exposed male C57BL/6J mice.[58, 59] One severe limitation of the study by Huang et al. is that they did not assess whether ketosis was necessary to induce the behavioral change.[59] However, similar results were replicated in a study that conducted two parallel experiments, in which a group of male ICR mice

received daily β-HB injections (300 mg/kg), another group received a ketogenic diet, and both were exposed to severe stressors and compared to separate controls.[60] The results of this study demonstrated that exogenous β-HB improved depressive behaviors, and mitigated the reduction of Histone3-lysine9-β-hydroxybutyrylation (H3k9βhb) and BDNF. Another animal study examined the offspring of female CD-1 mice that had followed a ketogenic diet during gestation and found that prenatal exposure to a ketogenic diet altered the offspring's' neuroanatomy and improved their resistance to the development of anxiety and depression in adulthood.[61] The primary changes to neuroanatomy in these offspring compared to controls were cerebellar volumetric enlargement by 4.8%, a hypothalamic reduction by 1.39%, and a corpus callosum reduction by 4.77%, relative to total brain volume. In human-based studies, ketogenic diets have been shown to have varying effects on mood and behavior in comparison to low-fat diets, such as decreasing markers of anxiety, but not affecting those of depression[62], demonstrating higher levels of fatigue, but lower levels of social antagonism[63], and impairing memory performance, but supporting sustained attention.[64] A study conducted in a human sample by Halyburton et al. compared the effects of a low-carbohydrate ketogenic diet to a high-carbohydrate diet on mood and cognitive performance.[65] These researchers showed that both diets were effective in improving mood, with no difference in effectiveness, but that the low-carbohydrate ketogenic diet improved cognitive processing speed more than the other dietary intervention. However, the generalizability of this study is limited to "healthy, overweight and obese, young to middle-aged adults with normal mood state and no cognitive impairment", and not populations with diagnosed MDD.[65] This literature review is expected to further

elucidate the influence of the ketogenic diet on improving characteristics of mood that are specifically affected in individuals with MDD.

Obesity and the Ketogenic Diet.

While the primary purpose of this narrative review is to outline the therapeutic potential of a ketogenic diet in treating MDD, it also seeks to confirm previously demonstrated effects of the ketogenic diet on body composition, especially in overweight and obese populations. Because of the elevated risk for these populations to develop MDD, other psychiatric disorders, and chronic metabolic diseases, it would be beneficial to identify treatments that improve both mental and metabolic health conditions. Within the literary body of evidence, there is varying data regarding the effectiveness of the low-carbohydrate ketogenic diets in comparison to other traditional weight-loss dietary interventions. Numerous studies of the ketogenic diet have demonstrated significantly greater improvements in weight loss and reductions in abdominal and visceral obesity in comparison to low-fat [66-74] and Mediterranean[75] diets. A follow-up study by Dyson et al. determined that the weight loss effect of the ketogenic diet was higher than that of a low-fat diet immediately following the intervention and at 6 months, but that this effect was no longer significantly different at two years after the intervention.[76] Several studies have shown improvements in body weight and obesity with the ketogenic diet but without any comparison to a control group.[77-80] The primary theory regarding the greater effectiveness of the ketogenic diet for weight loss is that they work indirectly by restricting total energy intake due to sustained satiety and energy expenditure, increased fatty acid oxidation, and a sparing effect on fat-free mass.[81] In contrast to this data supporting the efficacy of the ketogenic diet, numerous studies also demonstrate that

while the ketogenic diet does induce weight loss, it is no more effective than low-fat, the Mediterranean, or non-ketogenic low carbohydrate diets for the treatment of obesity.[72, 81-93] The primary theory for the ketogenic diet having no greater effectiveness than other traditional weight-loss diets is that all weight-loss diets have relatively similar total energy intakes and that there is no metabolic advantage to one or more particular macronutrients. The correlation between MDD and obesity supports further research into and the utilization of therapies like the ketogenic diet that can improve both conditions through multiple physiological mechanisms.

Biomarker Alterations with the Ketogenic Diet.

The association between biomarkers such as serum lipids and glucose and the oxidative stress and inflammation induced through MDD and chronic metabolic diseases has been well established. However, the evidence for the impact of a ketogenic dietary intervention on these biomarkers is highly ambiguous. Based on numerous studies examining the use of the ketogenic diet for weight-loss intervention and improvement of metabolic risk factors, it has been shown that the ketogenic diet has more significant effects on lipid profiles, glycemic control, and insulin resistance, and proinflammatory markers compared to traditional weight-loss diets. Some studies have shown a serum lipid response to a ketogenic diet that includes an increase in total cholesterol,[75, 81] low-density lipoprotein (LDL),[66, 75, 79, 83, 90-93] high-density lipoprotein (HDL),[66, 69, 74, 75, 77, 79, 80, 83, 90, 92-94] and a decrease in triglycerides (TG).[66, 74, 75, 77, 82-85, 93-97] Other studies have shown different effects on serum lipids leading to unchanged or decreased HDL,[73, 77, 79, 89, 95] TGs,[73, 79, 80] total cholesterol,[69, 73, 74, 77, 80, 94, 98] and LDL.[69, 73, 74, 80, 94-97] The alterations to glycemic control consistently show decreased serum glucose[69, 75, 84, 85, 90, 92,

[94] or glycated hemoglobin (HbA1c),[82] decreased insulin,[69, 79, 90, 92] and decreased insulin resistance.[85, 86, 98] The inflammatory markers that may be decreased in individuals following a ketogenic diet include TNF-α,[97, 99, 100] interleukin-6,[97, 100] interleukin-8,[97] monocyte chemoattractant protein 1 (MCP1),[97] E-selectin,[97] intercellular adhesion molecule 1 (I-CAM),[97, 100] and C-reactive protein (CRP).[90, 97, 100] However, Cardillo et al. found no change in serum CRP following a ketogenic dietary intervention.[99] These biomarkers are an important indicator of health as they are correlated with chronic stress and inflammation that can lead to the development of comorbid metabolic and psychiatric conditions. Based on the research regarding the influence of the ketogenic diet on metabolic biomarkers, the ketogenic diet may be beneficial for individuals with issues of glycemic control; however, there is no consensus regarding improvements to lipid markers as an effect of the ketogenic diet. Further research could provide valuable data to this area of literature, specifically by examining the effects of the ketogenic diet on these biomarkers in populations with MDD and other mood disorders.

Study Justification

The purpose of this review is to demonstrate the potential of the ketogenic diet to be utilized as a medical nutrition therapy for MDD. To the knowledge of the researchers, no past reviews have outlined how the ketogenic diet could functionally affect these physiological mechanisms of MDD. This narrative review briefly illustrates the prevalence of MDD, describes the physiological changes that occur from the condition, and identifies the increased risk for the development of obesity and other metabolic diseases. Animal models have shown the capability for the use of this diet as nutrition therapy for MDD through utilization of lipid metabolites in brains with altered glucose

metabolism, increased BDNF activity, and improved antioxidant capacity in the brain. These physiological effects of the ketogenic diet support its utilization in research for populations that have MDD and comorbid psychological and metabolic conditions. The current state of literature presents an opportunity for psychology and nutrition researchers to progress from animal models to examine whether these effects are observable in a human population while further assessing mood and the psychological characteristics of MDD. Furthermore, the advancement of knowledge in this area may help mental health care providers and nutrition professionals to better address the individual needs of their patients with MDD.

Chapter II. Methodology

This research project was originally designed as a randomized controlled trial to examine whether a 12-week high-fat, low-carbohydrate ad libitum ketogenic diet alone reduces depression severity and improves body composition more effectively than an ad libitum Dietary Approaches to Stop Hypertension (DASH) diet in a population of military veterans. However, due to the COVID-19/coronavirus pandemic at the beginning of 2020, this study was terminated and transitioned to a literature review to eliminate any risk of infection for participants and researchers. The provided approved methodology describes the processes through which the original dietary interventions were supposed to be conducted.

Participants

Initially, a total of 50 male and female veterans were expected to be recruited by public advertisement to participate in a 12-week dietary intervention. After Institutional Review Board (IRB) approval, participants were recruited from the Martinsburg Veterans Affairs Medical Center and its community-based outpatient clinics in the Shenandoah Valley region of Virginia through recruitment flyers and a bulk email distributed to James Madison University faculty, staff, and students (Appendix A). The primary inclusion criterion for participation was status as a veteran of any branch of the United States Armed Forces. Before recruitment was discontinued due to the COVID-19 pandemic, a total of 15 eligible individuals contacted the researchers; however, after being provided with an outline of the study participation requirements only 7 males and 1 female (n=8) elected to proceed with the informed consent. Participants were assessed for the presence and severity of major depressive disorder through the Beck Depression

Inventory-II (BDI-II) (Appendix B). Before the study commencement, all participants completed a health screening questionnaire (Appendix B), which was used to determine whether they met the inclusion and exclusion criteria. One additional inclusion criterion was for participants to be between the ages of 18-65 years. Participants were also eligible to be included if they had a diagnosed anxiety disorder or post-traumatic stress disorder, so long as major depression was a primary diagnosis as determined by a physician or mental health professional. The use of antidepressants or anxiolytics was allowed if the participant had been consistently using these medications for ≥ 8 weeks. Any change in antidepressant or anxiolytic medication type during the intervention would disqualify participants from continued participation. Participants were also able to use antidiabetic (including insulin), antihyperlipidemic, or antihypertensive medications if they have been consistently taken for ≥ 2 weeks, ≥ 8 weeks, and ≥ 2 weeks, respectively. Exclusion criteria included: weight instability (± 4.5 kg in the past 6 months); use of a low or no carbohydrate diet in the past 3 months; diagnosis of any psychological disorders other than major depressive disorder, an anxiety disorder, or post-traumatic stress disorder; use of mood stabilizers or antipsychotics.

The protocol and the potential risks and benefits of the study were fully explained to all participants before they provided written informed consent. All experimental procedures were approved by the IRB of James Madison University.

Study Design

In a parallel study design, eligible participants were randomly assigned to follow an ad libitum low-carbohydrate ketogenic dietary intervention (LCKD) or ad libitum Dietary Approaches to Stop Hypertension (DASH) for 12 weeks. Except for the

prescribed dietary intervention, participants were asked to maintain their usual lifestyle and activity throughout the study. At baseline (week 0), week 6, and week 12, participants would attend testing after an overnight fast. Details of the data collection methods for this testing are discussed in the following sections.

Dietary Intervention

Although both dietary interventions were prescribed as ad libitum, participants were provided general information about adequate nutrition practices. The estimated macronutrient distribution for each dietary intervention is as follows: the LCKD with 25-30% of total energy as protein, 65-70% as fat, and 5-10 % as carbohydrate; the DASH with 15-20% of total energy as protein, 30-35% as fat, and 50-55% as carbohydrate. Participants in the LCKD group were to be restricted to < 50g of total carbohydrates per day throughout the 12-week intervention to maintain their state of ketosis. To facilitate dietary compliance, participants in both groups received individualized handouts containing recipes, online resources, a list of foods that could assist them in meeting their nutritional needs and foods that should be avoided, and tips for maintaining their assigned dietary intervention (Appendix C). A consecutive four-day food record (3 weekdays, 1 weekend day) was to be collected and analyzed at weeks 0, 4, 8, and 12 either during an in-person meeting or phone call. This analysis was to be conducted using the Nutrition Data System for Research (NDSR) software (University of Minnesota Nutrition Coordinating Center, Minneapolis, MN). Additionally, participants assigned to the LCKD were supposed to complete a weekly dietary compliance checklist to ensure adherence to the assigned diet. If participants consumed any of the listed carbohydrate-containing foods, they would log what foods and how much was consumed and report

this information to the researchers at the end of each week. These checklists were intended to be used by researchers to assess participants' adherence to the assigned dietary guidelines and to prompt a personalized dietary education session to guide the participant back into dietary compliance if needed.

Clinical Measures

Body height was measured to the nearest 0.1 cm and body weight was measured to the nearest 0.05 kg using a MedVue® medical weight analyzer with a stadiometer (Detecto; Missouri). Both measures were taken while participants were barefoot and in light clothing. Body composition, specifically fat mass, fat-free mass, and body fat percentage were assessed using a dual-energy X-ray absorptiometry (DXA) scan (Illuminatus DXA, Norland at Swissray; Fort Atkinson, WI), while participants were supine in light clothing with no metal or footwear. Blood pressure was assessed by researchers using a sphygmomanometer, in a supine position, immediately following the DXA scan. Blood pressure measurement procedures followed the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription.[101] These clinical measures were to be collected at weeks 0, 6, and 12.

Questionnaires

The severity of major depressive disorder was assessed using the Beck Depression Inventory-II (BDI-II), which is a 21-question self-report inventory and a reliable and well-validated measure (Appendix B).[102] A high score on the BDI-II indicates a higher severity of the depressive state. The presence and severity of anxiety were assessed using the Beck Anxiety Inventory (BAI), which is a 21-question self-report inventory that is also a reliable and well-validated measure (Appendix B).[103] The

International Physical Activity Questionnaire-Long Form (IPAQ-L) is a self-administrable, 27-question measure, which produces estimates of physical activity in five domains: work, transportation, household, leisure, and sedentary time (Appendix B). The IPAQ-L has demonstrated good reliability and validity in research.[104] These questionnaires were to be completed by the participants during the laboratory testing sessions at weeks 0, 6, 12.

Biochemical Analysis

Fasted capillary blood samples were collected through fingersticks using blood lancets. Fasting blood glucose, a full serum lipid profile [including high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), total cholesterol], and serum ketone measures were taken and analyzed using a CardioChek PLUS Blood Analyzer (PTS Diagnostics; Indiana) and the appropriate testing strips. These measures were to be completed at weeks 0, 6, and 12. Additionally, urinary ketones were to be self-assessed daily by participants assigned to the LCKD, using URiSCAN® Ketones Urine Test Strips (YD Diagnostic Corp; South Korea). These results were to be recorded in a written log and provided weekly to researchers to assess the presence of ketosis and ensure LCKD dietary compliance. Each week, LCKD participants were expected to meet compliance with ketosis (positive urinary ketone test) for ≥ 6 days, or they would be removed from the study.

Statistical Analysis

The sample size was determined using the National Statistical Service Sample Size Calculator (Australian Bureau of Statistics). The confidence level was set at 95%. Based on the total population of U.S. military veterans (n=4,914,208), any sample of

these individuals is expected to yield a 0.069 proportion of individuals with MDD.[105] It was determined that the sample size for this study requires a minimum of 25 and a maximum of 99 participants to achieve confidence intervals of 0.10 and 0.05 respectively.

Before hypothesis testing, data was to be examined for normality using the Shapiro-Wilk test. Statistical analyses were to be performed with SPSS software (version 26.0; IBM; New York). Between-group differences in baseline characteristics were to be assessed using independent t-tests for continuous variables and Pearson chi-square test for categorical variables. The effects of the dietary intervention on psychological and biochemical variables were to be determined using repeated-measures analysis of variance (ANOVA) with time as the within-subject factor and diet (LCKD vs. DASH) and sex as between-subject factors. Statistical significance was to be set at $P < 0.05$.

Chapter III. Manuscript

Therapeutic Potential of a Ketogenic Diet in the Treatment of Major Depressive Disorder: A Narrative Review

ABSTRACT

Major depressive disorder (MDD) is the second most common mental health condition and a leading cause of disability in the world. It is theorized that MDD develops from a combination of biological, psychological, and social stressors. The condition is typically treated using pharmaceuticals and psychotherapy. However, not all individuals with MDD have access to or choose to use these treatments, or may prefer to incorporate therapeutic lifestyle changes such as exercise, sleep, and healthy eating. Even with treatment, MDD can alter brain structure and function, leading to the development of comorbid mental health and chronic metabolic conditions like obesity, cardiovascular disease, or diabetes. Physiological mechanisms that can be significantly affected by MDD episodes include brain glucose metabolism, brain-derived neurotrophic factor (BDNF) production and activity, and antioxidant function. This paper reviews existing literature to examine these components of the pathophysiology of MDD and outline how treatments could functionally improve the condition. Most research has examined the relationship between nutrition and MDD utilizing traditional interventions, like low-fat diets, but more recent studies have explored alternative nutrition therapies. Animal-models have shown potential for the use of the ketogenic diet as nutrition therapy for MDD by demonstrating improved metabolism of alternative nutrients, increased BDNF activity, and improved antioxidant capacity in the brain. However, to date, there are no studies that examine the effects of a ketogenic diet on a human population with MDD.

Future research is warranted to determine whether a ketogenic diet is a safe and reliable medical nutrition therapy for MDD.

INTRODUCTION

Major depressive disorder (MDD), also known as clinical or major depression, has a significant impact on the personal, social, familial, and occupational function of millions of individuals in the US and the rest of the world. According to the World Health Organization (WHO), MDD was the fourth highest cause of disability in the world in 2013 and is on course to be the second highest by the end of 2020.[1] While the global lifetime incidence of MDD has been estimated to be between 15 to 20%, there was a 10-year prevalence rise from 6.6% in 2005 to 7.3% in 2015.[1, 2] The incidence of MDD among the general population is based on a variety of demographic, socioeconomic, and lifestyle factors. Research has also revealed that depression is two to three times more common in individuals who already have multimorbidities compared to those with one or no chronic physical conditions.[3] This data indicates a potential risk for a cyclical or synergistic pattern of depression and chronic disease, due to the inflammatory effect that depression has on human physiology.

With research indicating that diet, sleep, and exercise all have a significant impact on the development, progression, and management of depression, there is an opportunity for creating non-pharmacological interventions that address these factors, especially among those individuals not currently following any treatments for depression.[4] To date, most research examining how nutrition can improve mental health has utilized dietary interventions that emphasize a higher intake of fruits, vegetables, and whole grains, following a low-fat diet or exchanging high saturated fat foods for those high in

unsaturated fats, or limiting the consumption of foods that are highly processed or contain high amounts of added sugars.[5] However, with the continued rise in the prevalence of MDD, it would be beneficial to continue research into the effects of nontraditional dietary interventions that do not necessarily strictly follow to these typical eating patterns. Therefore, this narrative review will describe the pathophysiology of MDD, including brain nutrient metabolism and oxidative stress, and the relationship between MDD and obesity. Additionally, it will review current research regarding the high-fat, low-carbohydrate ketogenic diet and its mechanistic action on neurophysiological systems that are dysregulated in MDD to outline the therapeutic potential of this type of dietary intervention in the treatment of the condition.

METHODS

An initial literature search was conducted between February 5, 2018 and May 4, 2018, in addition to an updated search between March 2, 2020 and June 5, 2020, using three databases. The databases (PubMed, Cumulative Index to Nursing and Allied Health Literature [CINAHL], and Cochrane Library) were searched using the following terms either singularly or in combination: *Ketogenic Diet, Ketone Metabolism, Major Depressive Disorder* or *Depression*, *Brain-derived Neurotrophic Factor*, *Oxidative Stress*, and *Obesity*. The review includes intervention studies with no restrictions on the population examined but is limited to research published after January 1, 2000 and written in the English language. Articles were excluded if the primary dietary intervention utilized a low carbohydrate non-ketogenic diet or exogenous ketone source, or if the sample size was less than 50 human participants. The research design was not a factor for exclusion, due to the variability of methodologic limitations or the lack of

control groups within the reviewed studies. Figure 1 summarizes the processes of this literature search, and Table 1 presents a summary of the literature.

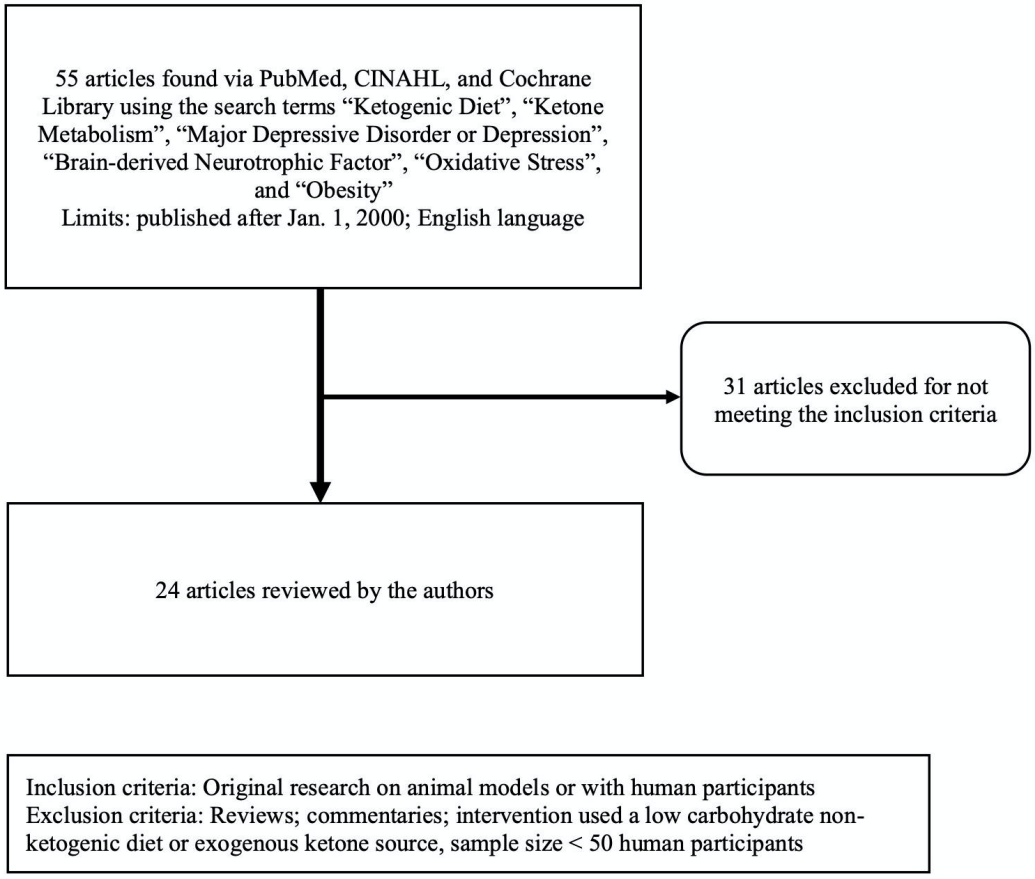

Figure 1. Flow diagram of literature review processes evaluating the relationship between the ketogenic diet and major depressive disorder.

DISCUSSION

Neuropathology of Major Depressive Disorder

To better comprehend the prevalence and effects of MDD, it is important to understand its status as a mental health condition and how it is categorized and diagnosed by mental health professionals. MDD is classified as a neuropsychiatric mood disorder and is characterized by a persistently depressed mood or loss of interest in daily

activities.[6] A diagnosis typically designates the condition as either an isolated or recurrent episode, and will classify the episode as mild, moderate, or severe.[6] MDD is considered to be caused by a combination of various biological, psychological, and social stressors, which can create an inflammatory state within the body that affects multiple physiological organ systems. These factors can also alter some of the major brain functions including brain glucose metabolism, regulation of brain-derived neurotrophic factor (BDNF), and antioxidant activity.

Glucose metabolism. Although glucose is typically the main source of energy for the brain, there are significant alterations in the mechanisms of glucose metabolism in populations affected by major depression. Several studies examining individuals with MDD have demonstrated regional glucose hypometabolism and metabolic asymmetry in various regions of the brain, including the left prefrontal cortex, cerebellum, left anterior cingulate, right insular cortex, right claustrum, right anteroventral caudate and putamen, right middle temporal gyrus, and right superior temporal gyrus.[7-9] These alterations have been associated with the progression of depressive episodes as individuals with more severe depression have demonstrated lower global cerebral glucose metabolic rates.[10] It has also been shown that successful pharmacological treatment with various antidepressants can increase glucose utilization in the left prefrontal cortex; although, this may not improve whole frontal glucose metabolism.[8] Holthoff et al. even reported decreases in regional glucose metabolism in remitted MDD patients treated with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).[7] These results demonstrate that specific antidepressant treatments may not induce long-term changes to or may have detrimental effects on cerebral glucose

metabolism**.** A possible causal link between MDD and decreased cerebral glucose metabolism was illustrated by Kahl et al. showing that elevated DNA methylation of GLUT1 in unremitted MDD patients lowered GLUT1 expression in brain cells, but could be reversed through MDD remission.[11] These findings indicate that glucose uptake from blood vessels into the brain may be compromised in both untreated and treated MDD and suggest that the utilization of other energy sources could potentially improve cerebral metabolism for these individuals.

BDNF. Although brain metabolic dysfunction is an important factor in the pathophysiology of depression, there are other noted alterations in brain function, such as changes to the activity of BDNF. BDNF is the most abundant neurotrophin in the nervous system and is involved in the development and regulation of neuronal systems, neurotransmitter activity, and neuroplasticity.[12, 13] Individuals with MDD have been shown to have significantly lower concentrations of serum BDNF in comparison to healthy controls.[12, 14-19] Lower serum BDNF levels have also been reported during recurrent depressive episodes as compared to first episodes,[14] in individuals with long-term MDD (≥1 year) as compared to short-term MDD (<1 year),[20] and in individuals with MDD as compared to individuals with dysthymia.[17] Sözeri-Varma et al. did find one contrasting result by demonstrating that there was no significant difference in serum BDNF levels between individuals in their first and recurrent MDD episodes.[15] Regarding the correlation between MDD treatment and BDNF activity, it has been demonstrated that antidepressants can increase serum BDNF levels in individuals with MDD.[12, 16, 19] While these findings do not indicate that antidepressants only treat MDD by improving BDNF levels, it has been suggested that low BDNF levels play an important role in the

pathophysiology of MDD and other affective disorders.[12, 16, 19] Although most data appears to support this hypothesis, there is no evidence for directionality in this relationship, and some conflicting data has been shown between serum BDNF levels and the severity of MDD.[14, 15, 20] The correlation between improvements to reduced BDNF levels and the severity of MDD symptoms warrants additional research, especially regarding treatments and interventions that can improve both of these conditions.

Oxidative Stress. Other prevalent alterations to brain function in MDD can occur through the action of oxidative stress, which can have significant effects on brain structure and metabolism, and neuronal interaction. Markers of oxidative stress and reduced antioxidant function have been repeatedly noted in individuals with MDD compared to healthy controls.[21-25] The major brain antioxidant glutathione, its complementary enzyme glutathione peroxidase (GPx), and the detoxifying brain isozyme glutathione S-transferase Mu 1 (GST Mu 1) were shown to be significantly lowered in post-mortem brain tissues of individuals with MDD, bipolar disorder, and schizophrenia[21, 26] and the serum of living individuals with MDD.[22, 25] However, there has been a report that found no difference in GPx activity between individuals with MDD and healthy controls.[23] While these enzymes are typically reduced during MDD, there have also been some reports of increased activity of the antioxidant enzymes glutathione reductase,[22, 26] superoxide dismutase (SOD),[22, 26, 27] and catalase.[23, 27] However, Rybka et al. did find decreased SOD activity in individuals with MDD in comparison to healthy controls.[25] Additionally, some of these antioxidant activities have not been shown to improve or have been slightly suppressed with the pharmacological treatment of MDD.[23, 26, 27] These findings illustrate that oxidative stress in psychiatric conditions, including

MDD, is likely exacerbated by antioxidant dysregulation and dysfunction. Markers of oxidative stress, such as malondialdehyde, 8-OH 2-deoxyguanosine, interleukin-6, tumor necrosis factor-α (TNF-α), F2-isoprostanes, neopterin have also been found in elevated levels in individuals with MDD, and some have been associated with decreased effectiveness of antidepressant treatments.[24-26] Interleukin-6 levels, however, have been shown to decrease with SSRI treatment.[24] The relative ineffectiveness of several antidepressant treatments for improving oxidative stress in MDD suggests that other therapeutic methods should be examined for the limitation of prooxidant and enhancement of antioxidant systems.

Obesity. Due to its similar relationship with increased oxidative stress and systemic inflammation, it is important to also examine obesity and how it correlates with MDD. There have been numerous large-scale, cross-sectional epidemiological and observational studies that have examined this relationship, and have demonstrated a positive correlation between obesity and MDD.[28-32] Several studies have reported that this association occurs mainly between MDD and severe or class III obesity (body mass index ≥ 40 kg/m^2).[28, 33, 34] Despite this significant correlation, no causal direction of the MDD-obesity relationship has been officially established. It has been shown that the presence of overweight or obesity in individuals with MDD can significantly slow their clinical and neuroendocrine responses to antidepressant treatment.[35] Additionally, weight loss has been associated with a significant, sustained reduction in the severity of MDD, with individuals achieving greater weight loss also experiencing the largest reduction in MDD severity.[34] The importance of treating MDD is further emphasized by the correlation between the presence of a current or lifetime MDD diagnosis, in addition to

obesity, and an increased risk for the development of other psychiatric disorders, smoking, physical inactivity, alcohol and substance abuse, disordered eating, and other unhealthy behaviors.[28, 30] Although these findings did not determine a specific causal direction in the MDD-obesity relationship, they do suggest the dire need for a multifactorial and comprehensive approach to the treatment of MDD and obesity, beyond pharmaceuticals, especially when the conditions are concurrently present.

Effects of a Ketogenic Diet on Neurophysiology

Traditional treatments for MDD may not always be effective in managing physiological consequences of the condition, especially reduced glucose metabolism in the brain, decreased BDNF levels, increased levels of oxidative stress, or comorbid chronic diseases. A possible alternative or complementary treatment for MDD would be a dietary intervention focusing on the ketogenic diet, which is a high-fat, very low-carbohydrate, adequate-protein eating plan. Typically, it includes an initial reduction of net carbohydrate intake to less than 20-50 grams per day with a macronutrient distribution of approximately 0-10% carbohydrate, 60-80% fat, and 10-30% protein as a percent of total energy intake.[36] This severe restriction of carbohydrates imitates a "fasted state" by lowering glucose availability, which decreases insulin and increases glucagon concentrations and creates a metabolic shift in the body from fat storage to lipolysis and β-oxidation.[37] However, in the ketogenic diet, both exogenous and endogenous protein and fat sources can provide energy, and glucose concentrations can be relatively maintained without carbohydrate intake.[36] The ketogenic diet's alternative nutrient utilization is one of its most important characteristics and may be beneficial for individuals with MDD as they typically have reduced glucose metabolism in the brain.

The subsequent sections describe the mechanisms of action related to the ketogenic diet in brain nutrient metabolism, the production of BDNF, regulation of oxidative stress, and weight management that could improve some of the other physiological consequences of MDD.

Ketone Metabolism. As the ketogenic diet restricts carbohydrate intake to a level at which the body is not able to maintain carbohydrate utilization throughout all tissues, it is necessary that the body more effectively use lipids and their metabolites for energy. When energy is mainly provided by fatty acid oxidation in cell mitochondria, large amounts of acetyl-CoA are produced, which are then utilized, primarily in the liver, to synthesize the ketone bodies β-hydroxybutyrate (β-HB), acetoacetate and acetone.[38] Ketosis occurs when the metabolic efficiency of the Krebs, or tricarboxylic acid (TCA) cycle, is reduced and additional acetyl-CoA is converted into ketones.[38] Because the liver does not have succinyl CoA:3- ketoacid CoA transferase, a mitochondrial enzyme that converts acetoacetate to acetoacetyl CoA, ketone bodies are forced into the circulatory system.[39] In ketosis, the levels of the ketone bodies β-HB, acetoacetate, and acetone are increased in the peripheral blood and urine. These ketones are delivered to and serve as a fuel source for numerous extrahepatic tissues, including the brain.[38, 40] Higher levels of ketosis will proportionally spare glucose from metabolism in the brain and other tissues.[40] This mechanism has great significance in conditions in which glucose availability can be severely limited, as fatty acids are not able to cross the blood-brain barrier to provide energy. This sparing effect of ketones for glucose in cerebral metabolism has been shown in rat models and has demonstrated a coordinated upregulation of energy metabolic genes and an increase in metabolic gene transcripts.[40, 41]

To the knowledge of the researchers, no current research has demonstrated these findings in any human population. Despite this lack of research, the ketogenic diet provides an alternative source of energy for the brain, which could benefit individuals with MDD who experience significantly reduced brain glucose metabolism.

BDNF Activity and the Ketogenic Diet. Another aspect of brain function affected by ketone bodies is the concentration and activity of BDNF. Although no studies have demonstrated *in vivo* action of ketones on the expression of BDNF in humans, *in vivo and vitro* animal models have shown ketone-mediated alterations in BDNF gene expression and protein levels.[42-44] Genzer et al. showed an increase in the BDNF:proBDNF ratio, whole brain and liver BDNF expression, and BDNF mRNA in a population of C57BL/6 male mice fed an *ad libitum* ketogenic diet.[42] This finding suggests a ketone-induced upregulation of BDNF production, especially in the brain. However, Vizuete et al. demonstrated that BDNF content was decreased in the corpus striatum, but not the hippocampus, in male Wistar rats fed a ketogenic diet.[44] These conflicting results imply that a ketogenic diet may affect BDNF regulation by increasing total BDNF gene expression and content but reducing regional BDNF synthesis. In an *in vitro* study of exercised male C57BL/6 mice, β-HB was found to increase with exercise and coincided with an increase in BDNF expression and protein levels in cortical neurons.[43] This finding is consistent with the results of the previously discussed *in vivo* studies, as it suggests that β-HB is involved in the *in vivo* regulation of BDNF. Although these studies have only examined animal models, they indicate that there could be benefits of using a ketogenic diet in conditions like MDD, in which BDNF expression or protein levels are lowered.

Oxidative Stress and the Ketogenic Diet. In addition to the previously mentioned metabolic and neurological alterations, the ketogenic diet has been shown to have significant impacts on both systemic and brain oxidant-antioxidant systems. The theorized neuroprotective effect of the ketogenic diet is associated with acetoacetate and β-HB and has only been demonstrated in animal models. These studies have shown that a ketogenic diet, via acetoacetate and β-HB action, can protect hippocampal and dopaminergic neurons from glutamate-induced or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) excitotoxicity and can increase glutathione synthesis and NAD(P)H dehydrogenase quinone 1 (NQO1) activity.[45-47] The upregulation of these antioxidant substrates could contribute to the ketogenic diet's protective mechanism against oxidative damage and improvements in mitochondrial redox status. An animal study showed the indirect effects of the ketogenic diet in mediating oxidative stress by decreasing the production of reactive oxygen species (ROS) and increasing gene expression of cytosolic and mitochondrial antioxidants.[47, 48] It is suggested that the reduction in ROS production is achieved by improving mitochondrial uncoupling protein activity, which reduces the membrane potential upon which the ROS production is dependent.[48] The ketogenic diet has also been shown to improve hippocampal mitochondrial antioxidant capacity, specifically by increasing NQO1, SOD, and GPx expression and decreasing catalase activity in animal models.[49, 50] These animal-based studies demonstrate that the ketogenic diet has the potential for reliable antioxidant, anti-inflammatory, and neuroprotective capabilities in conditions, like MDD and obesity, that are adversely affected by systemic and neural oxidative stress and inflammation.

However, more research is needed to determine if the ketogenic diet can reliably improve antioxidant capacity and reduce oxidative damage in humans.

Mood Changes with the Ketogenic Diet. Several animal studies have demonstrated possible antidepressant or mood-improving properties of the ketogenic diet; however, the exact mechanisms have not been established. One of these studies appeared to show that a ketogenic diet, mainly through the action of β-HB, reduced "behavioral despair" in stressor-exposed male Wistar rats.[51] Another animal study examined the offspring of female CD-1 mice that had followed a ketogenic diet during gestation and found that prenatal exposure to a ketogenic diet altered the offspring's neuroanatomy and improved their resistance to the development of anxiety and depression in adulthood.[52] The primary changes to neuroanatomy in these offspring compared to controls were increased cerebellar volume and a reduction in the hypothalamic and corpus callosum. A study conducted in a human sample by Halyburton et al. compared the effects of a low-carbohydrate ketogenic diet to a high-carbohydrate diet on mood and cognitive performance.[53] These researchers showed that both diets were effective in improving mood, with no difference in effectiveness, but that the low-carbohydrate ketogenic diet improved cognitive processing speed more than the other dietary intervention. However, the generalizability of this study is limited to "healthy, overweight and obese, young to middle-aged adults with normal mood state and no cognitive impairment", and not populations with diagnosed MDD.[53] Further research is warranted to determine the influence of the ketogenic diet on improving characteristics of mood that are specifically affected in individuals with MDD.

Obesity and the Ketogenic Diet. While the primary purpose of this narrative review is to outline the therapeutic potential of a ketogenic diet in treating MDD, it also seeks to confirm previously demonstrated effects of the ketogenic diet on body composition, especially in overweight and obese populations. Because of the elevated risk for these populations to develop MDD, other psychiatric disorders, and chronic metabolic diseases, it would be beneficial to identify treatments that can improve conditions that affect both mental and metabolic health. Within the literary body of evidence, there is varying data regarding the effectiveness of the low-carbohydrate or ketogenic diets in comparison to other traditional weight-loss dietary interventions. Several studies of the ketogenic diet have demonstrated significantly greater improvements in weight loss and reductions in abdominal and visceral obesity in comparison to low-fat diets.[54-56] In contrast to this data supporting the efficacy of the ketogenic diet, numerous studies also demonstrate that while the ketogenic diet does induce weight loss, the diet's effect is no different than that of a low-fat diet for the treatment of obesity.[57-62] The primary theory for the ketogenic diet having no greater effectiveness than other traditional weight-loss diets is that all weight-loss diets have relatively similar total energy intakes and that there is no metabolic advantage to one or more particular macronutrients. The correlation between MDD and obesity supports further research into and the utilization of therapies like the ketogenic diet that can improve both conditions through multiple physiological mechanisms.

Biomarker Alterations with the Ketogenic Diet. The association between biomarkers such as serum lipids and glucose and the oxidative stress and inflammation induced through MDD and chronic metabolic diseases has been well established.

However, the evidence for the impact of a ketogenic dietary intervention on these biomarkers is highly ambiguous. Based on numerous studies examining the use of the ketogenic diet for weight-loss intervention and improvement of metabolic risk factors, it has been shown that the ketogenic diet has more significant effects on lipid profiles, glycemic control, and insulin resistance compared to traditional weight-loss diets. Some studies have shown a serum lipid response to a ketogenic diet that includes an increase in low-density lipoprotein (LDL),[54, 57, 60, 61] an increase in high-density lipoprotein (HDL),[54, 57, 60-63] and a decrease in triglycerides (TG).[54, 56, 57, 59-62] Other studies have shown different effects on serum lipids leading to unchanged or decreased HDL,[59] total cholesterol,[56, 59, 62, 63] and LDL.[56, 59, 62, 63] Alterations to glycemic control typically show decreased serum glucose,[58, 60-63] decreased insulin,[60, 61] and decreased insulin resistance.[58, 63] These biomarkers are an important indicator of health as they are correlated with chronic stress and inflammation that can lead to the development of comorbid metabolic and psychiatric conditions. Based on the research regarding the influence of the ketogenic diet on metabolic biomarkers, the ketogenic diet may be beneficial for individuals with issues of glycemic control; however, there is no consensus regarding improvements to lipid markers as an effect of the ketogenic diet. Further research could provide valuable data to this area of literature, specifically by examining the effects of the ketogenic diet on these biomarkers in populations with MDD and other mood disorders.

CONCLUSIONS

This narrative review illustrates that MDD is a prevalent health condition that in addition to adverse mood and behavioral changes, results in numerous physiological alterations and creates a risk for the development of obesity and other chronic metabolic

diseases. It is of vital importance to develop novel therapies that have the potential to utilize multiple mechanisms of action to treat this condition with long-term success. The ketogenic diet is a specific intervention that could prove effective in reducing the severity of depression, improving body composition, and attenuating the effects of several chronic diseases. Although the ketogenic diet has been shown to have varying effects on mood in humans, animal models show promise in the use of this diet as nutrition therapy for MDD through alternate nutrient utilization of lipid metabolites, increased BDNF activity, and improved antioxidant capacity in the brain. The current state of literature presents an opportunity for psychology and nutrition researchers to progress from animal models to examine whether these effects are observable in a human population while assessing mood state and psychological characteristics of MDD.

The ketogenic diet may be beneficial for other diseases or disorders in which improvements in systemic inflammation also reduce the severity of the condition. The research concerning the effectiveness of the ketogenic diet for body composition improvement consistently demonstrates that the diet induces total weight and fat mass loss; however, conflict in the literature does exist as to whether the ketogenic diet is more effective than traditional weight-loss dietary interventions in the short- and long-term, and as to which populations would benefit from its implementation. As the ketogenic diet has rarely been shown to be less effective, it has potential use for populations with all levels of overweightness and obesity, although concerns with adherence and sustainability of this dietary pattern do exist. This narrative review has also demonstrated that the ketogenic diet can improve biomarkers of glycemic control and inflammation; however, there is some disagreement about its effect on lipid-based biomarkers of

cardiovascular disease. Future research should continue to examine the nutritional consequences of the ketogenic diet through the analysis of changes to metabolic biomarkers.

The potential physiological outcomes of the ketogenic diet support its application in research for populations that are at risk for or have comorbid psychological and metabolic conditions. Integration of the ketogenic diet into other lifestyle improvement and weight loss strategies may prove particularly effective for these populations as multifactorial approaches are more effective for treating comorbid conditions that affect multiple physiological systems. However, future research first needs to employ randomized controlled trials to thoroughly examine the short- and long-term psychological, physiological, and metabolic effects of a ketogenic diet in a population with MDD. These studies should consider possible confounding variables, such as psychiatric and metabolic comorbidities, previous antidepressant treatment, race and ethnicity, sex and gender, age, and previous use of other nutrition therapies. If the ketogenic diet proves to be safe, reliable, and effective as a nutrition therapy for MDD, further research could explore the different responses to the ketogenic diet based on the severity of MDD and length of the episode or history of recurrence, and should include a long-term follow up to assess the sustainability of these desire outcomes. Although further research is warranted before nutrition therapy recommendations can be established, both mental health and nutrition professionals should consider the therapeutic potential of the ketogenic diet for individuals with MDD or multimorbidities that are not receptive or responsive to traditional treatments.

Table 1. Studies investigating the ketogenic diet and characteristics of MDD

Reference	Design	Participants	Intervention	Primary Outcome(s)	Results/conclusions
Bazzano and colleagues (2014)[56]	RCT	148 adults Ages 22-75 y BMI 30-45kg/m^2	12-months diet Low carbohydrate diet (LCD): < 40 g carbohydrate / day Low Fat diet (LFD): < 30% of total kcal from fat, <7% from saturated fat	Body weight Fat mass Serum high-density lipoprotein (HDL) Serum Triglycerides (TGs) Plasma glucose Serum C-reactive protein (CRP)	LCD group experienced greater weight loss Fat mass decreased more in the LCD group HDL was increased more in the LCD group TGs were decreased more in the LCD group Plasma glucose was not changed for either group CRP was reduced more in the LCD group
Bough and colleagues (2006)[41]	RCT	57 male Sprague-Dawley rats, ~40 days old	3-week diet Kcal-restricted Ketogenic diet (KD): BioServ F3666 Normal, ad libitum control diet (Purina 5001)	Plasma Beta-hydroxybutyrate (β-HB) Plasma glucose Cerebral metabolites and nucleotides Enzyme activity Mitchondrial count	KD was associated with upregulation of metabolic gene transcripts (protein metabolism, glycolysis, tricarboxylic acid, oxidative phosphorylation) No difference in activity of energy metabolic enzymes between groups KD was associated with an increased number of mitochondrial profiles in the hippocampus KD was associated with hippocampal synaptic transmission that was resistant to low glucose availability
Brinkworth and colleagues (2009)[58]	RCT	107 adults Ages 18-65y Abdominal obesity and one metabolic syndrome risk factor	12-month diet Isocaloric diets with mild kcal restriction: 1430 kcal for females, 1675 kcal for males Very low carbohydrate diet (VLCD; 4% carbohydrate, 35% protein, 61% fat/20% saturated fat) Low fat diet (LFD; 46% carbohydrate, 24% protein, 30% fat)	Body weight Fat mass (FM) Fat-free mass (FFM) Plasma glucose Serum total cholesterol (TC) Serum High density lipoprotein (HDL) Serum Low density lipoprotein (LDL) Serum Triglycerides (TGs) Blood glucose	Both diets resulted in weight loss and a decrease in FM, with no differences between groups VLCD was associated with greater decrease in FFM than the LFD Blood glucose was decreased in both groups TC, LDL, HDL were increased more in the VLCD group TGs decreased more in the VLCD group
Dashti and colleagues (2004)[63]	Pre-test /Post-test	83 obese (39 males, 44 females) BMI > 35 kg/m^2	24-week ketogenic diet First 12 weeks: 20-30g total carbohydrate and 80-100g protein, emphasis on poly- and monounsaturated fats for fat intake Second 12 weeks: increase to 40-50 g carbohydrate Daily multivitamin/mineral	Body weight/BMI Serum total cholesterol (TC) Serum High density lipoprotein (HDL) Serum Low density lipoprotein (LDL) Serum Triglycerides (TGs) Blood glucose	Body weight decreased during all stages of diet TC, LDL, and TGs decreased from baseline to post-test HDL increased from baseline to post-test Blood glucose decreased from baseline to post-test

Table 1. Studies investigating the ketogenic diet and characteristics of MDD

Reference	Design	Participants	Intervention	Primary Outcome(s)	Results/conclusions
Gardner and colleagues (2016)[61]	RCT	61 adults Ages 18-50y BMI 28-40kg/m^2 Insulin resistant (IR) or sensitive (IS)	6-month diet Low Fat diet (LFD): 20 g fat / day Low Carbohydrate diet (LCD): 20 g digestible carbohydrate/ day 4 groups: LFD-IR, LFD-IS, LCD-IR, and LCD-IS	Body weight change Plasma High density lipoprotein (HDL) Plasma Low density lipoprotein (LDL) Plasma Triglycerides (TGs)	All diets experienced weight loss, but there was no difference between groups LDL decreased in both LFD groups, and increased in both LCD groups TGs decreased for all groups, but there was no difference between groups HDL increased for all groups, but there was no difference between groups Fasting glucose decreased for three groups, but not the LCD-IS group, and there was no difference between groups
Genzer and colleagues (2016)[42]	RCT	96 C57BL/6 male mice, 4wk old	2-week Ad libitum low-fat diet (LFD) 6 groups: 8-week ad libitum LFD, restricted feeding LFD (RF-LFD), high fat diet (HFD), RF-HFD, ketogenic diet (KD), or RF-KD	BDNF mRNA expression	HFD was associated with increases in brain and liver BDNF expression KD was associated with increases in BDNF:proBDNF ratio, whole brain and liver BDNF expression, and BDNF mRNA in the brain
Greco and colleagues (2016)[49]	RCT	36 male Sprague-Dawley rats 35 days old	6-24hours diet Ketogenic diet (8.4% protein, 78.8% fat, 0.8% carbohydrate, 5% fiber) Standard diet (18.6% protein, 6.2% fat, 59.8% carbohydrate, 4.8 fiber) Controlled cortical impact (CCI) surgery or placebo	3-nitrotyrosine (3NT) 4-hydroxynonenol (4-HNE) expression NAD(P)H dehydrogenase quinone 1 (NQO1) expression Superoxide Dismutase (SOD1 and 2) expression	Ketogenic diet was associated with decreased 3NT expression and increased 4HNE, NQO1 and SOD1 expression Ketogenic diet was associated with an increase in protein expression of cytosolic and mitochondrial antioxidants Ketogenic was associated with a decrease in markers of oxidative damage
Halyburton and colleagues (2007)[53]	RCT	121 adults, overweight or obese Age 24-64 y BMI 26-43 kg/m^2	8-week diet Low Carbohydrate High Fat (LCHF) diet (35% protein, 61% fat, 20% saturated fat, 4% carbohydrate) High Carbohydrate Low Fat (HCLF) diet (24% protein, 30% fat, <8% saturated fat, 46% carbohydrate) Both diets isocaloric and with 30% energy requirement restriction	Beck Depression Inventory (BDI) Profile of Mood States (POMS) Spielberger State Anxiety Inventory (SAI) Cognitive function: digit span backwards (DSB) and inspection time (IT) tests	LCHF diet was associated with an increase in plasma ketones LCHF diet group experience greater weight loss than the HCLF diet group Both diets should a significant improvement in BDI, POMS, and SAI scores, but there was no difference between groups DSB scores increased in both groups LCHF diet decreased IT score more than the HCLF diet
Jarrett and colleagues (2008)[47]	RCT	14 male P28 rats, adolescents	3-week diet Ketogenic diet (Bio-Serv F3666) Control Diet (Bio Serv F3517) Diets were isocaloric and 90% of daily requirements	Serum B-HB Glutathione (GSH) concentration Reduced coenzyme A (CoASH) levels Glutamate cysteine ligase (GCL) levels	Ketogenic diet was associated with an upregulation of GSH synthesis Ketogenic diet was associated with an increase in CoASH and GCL activity

Table 1. Studies investigating the ketogenic diet and characteristics of MDD

Reference	Design	Participants	Intervention	Primary Outcome(s)	Results/conclusions
Lim and colleagues (2010)[57]	RCT	104 adults 1 or more cardiovascular disease risk factor BMI 28-40 kg/m^2	15-month diet: 3 months with counseling, 12 months self-maintenance All diets 1550kcal Very Low Carbohydrate (VLC; 35% protein/60% fat/20% saturated fat/4% carbohydrate) Very Low Fat (VLF; 20% protein/10% fat /3% saturated fat /70% carbohydrate) High Unsaturated Fat (HUF; 20% protein/ 30% fat/ 6 saturated fat/8% polyunsaturated fat/ 50% carbohydrate) Control	Body weight Blood pressure (BP) Serum High density lipoprotein (HDL) Serum Low density lipoprotein (LDL) Serum Triglycerides (TGs) Blood glucose Plasma ketones	All diets, excluding control, experienced weight loss with no differences between groups VLC was associated with increases in LDL and HDL, while other diets decreased both factors VLC was associated with a decrease in TGs, while other diets increased this factor All diets, excluding control, experienced a decrease in BP with no differences between groups
Marosi and colleagues (2016)[43]	RCT	16 male C57BL/6 mice	6-week diet 2 groups: with (n=8) and without (n=8) running wheels Food and water ad libitum 12h light/12h dark cycle	Plasma 3-hydroxybutyrate (3-HB) concentration Neuronal oxygen consumption and glycolytic rate Neuronal BDNF concentrations	Higher 3-HB concentrations were associated with increases in neuronal oxidative metabolism and metabolic rate Higher 3-HB concentrations were associated with increased ATP production, NAD/NADH ratio, and mitochondrial electron transport chain activity Higher 3-HB concentrations were associated with increased BDNF mRNA and protein expression in low glucose concentration areas
Milder and colleagues (2010)[45]	RCT	12 male Sprague-Dawley rats	1-, 3-day or 1- or 3-week diets 12h light/dark cycle Water ad libitum Fasted 8-10 hours pre-diet Ketogenic diet (78% F, 0.76% C) or control (5% F, 65% C) kcal restrict to 90% daily requirements	NAD(P)H:quinone oxidoreductase (NQO1) activity 4-hydroxy-2-nonenal (4-HNE) Glutathione (GSH) Reduced coenzyme A (CoASH)	Ketogenic diet was associated with increased hippocampal GSH synthesis and NQO1 activity Ketogenic diet was associated with decreased CoASH and GSH
Murphy and colleagues (2004)[51]	RCT	40 adult male Wistar rats	7 day diet 2 groups: Ketogenic diet (n=20) and control (n=20) Food access 2.5 hours per day	Serum B-HB Porsolt Test: animal model of depression	Ketogenic diet was associated with an increase in serum B-HB Ketogenic diet was associated with better performance on the Porsolt test, indicating less behavioral despair Ketogenic diet may have antidepressant properties

Table 1. Studies investigating the ketogenic diet and characteristics of MDD

Reference	Design	Participants	Intervention	Primary Outcome(s)	Results/conclusions
Noakes and colleagues (2006)[60]	RCT	67 adults One or more cardiovascular risk factor BMI > 28 kg/m2[2]	12-week diet: 8-week intervention and 4-week weight maintenance Isocaloric diet 1450kcal Very Low Fat (VLF) (Carbohydrate%: Fat%: Protein%, %SF = 70:10:20; 3%) High Unsaturated Fat (HUF) = (50:30:20, 6%) Very Low Carbohydrate (VLC) (4:61:35, 20%)	Body Weight Fat Mass Lean Mass Serum total cholesterol (TC) Serum High density lipoprotein (HDL) Serum Low density lipoprotein (LDL) Serum Triglycerides (TGs) Blood glucose Fasting insulin	All groups experienced weight loss and lean mass loss, but there was no difference between groups All groups experience fat mass loss, but the VLC and VLF groups experienced greater reductions LDL and HDL were increased more in the VLC group compared to the other groups TGs were decreased in the VLC group compared to other groups Blood glucose did not change for any groups Fasting insulin was decreased more in the VLC group compared to the other groups
Samaha and colleagues (2003)[55]	RCT	132 adults Severely obese (BMI > 35kg/m^2)	6-month diet Low carbohydrate diet (LCD): < 30 g CHO/day, no restriction on fat intake Low fat diet (LFD): 500 kcal deficit, < 30% kcal from fat	Body weight Serum Triglycerides (TGs) Serum High density lipoprotein (HDL) Serum Low density lipoprotein (LDL) Fasting blood glucose	LCD was associated with greater weight loss compared to the LFD TGs were decreased more in the LCD diet Neither experienced a significant change in HDL or LDL Glucose levels were only significantly decreased in LCD participants who had diabetes
Stern and colleagues (2004)[59]	RCT	87 adults Severely obese (BMI > 35kg/m^2)	1-year follow-up Low carbohydrate diet (LCD): < 30 g CHO/day, no restriction on fat intake Low fat diet (LFD): 500 kcal deficit, < 30% kcal from fat	Body weight Serum total cholesterol (TC) Serum High density lipoprotein (HDL) Serum Low density lipoprotein (LDL) Serum Triglycerides (TGs) Blood glucose HbA1c	Both groups experienced weight loss but there was no difference between groups Changes in total cholesterol and LDL were not different between baseline and follow-up or between groups TGs decreased more in the LCD group HDL decreased in both groups, but was reduced more in the LFD group Changes in blood glucose were not different between baseline and follow-up or between groups HbA1c was lower for the LCD group only for participants with diabetes
Sullivan and colleagues (2004)[48]	RCT	45 C3HeB/FeJ mice	10-12 day diet Ketogenic diet (Bio-Serv F3666) (n=22) Standard diet (n=23) Food and water ad libitum	Serum B-HB Hippocampal mitochondrial respiration and Reactive Oxygen Species (ROS) production	Ketogenic diet was associated with an increase in serum B-HB levels Ketogenic diet was associated with an increase in hippocampal mitochondrial respiration rate Ketogenic diet was associated with decreased ROS production in hippocampi

Table 1. Studies investigating the ketogenic diet and characteristics of MDD

Reference	Design	Participants	Intervention	Primary Outcome(s)	Results/conclusions
Sussman and colleagues (2014)[52]	RCT	24 Male and female CD-1 parental mice 44 6-weeks old offspring mice	30-day diet for parent mice KD (67.4% fat, 0.6% carbohydrate, and 15.3% protein) or control (5% fat, 76.1% carbohydrate, and 18.9% protein) Ad libitum food and water Males and female naturally mated after diet ended Ketogenic diet (n=20) and control (n=24) offspring tested	Open-field test (locomotor activity and anxiety model) Forced-swim test (behavioral despair model) Exercise-wheel test (physical activity model)	Ketogenic diet was associated with reduced susceptibility to depression and anxiety and increased physical activity in offspring Ketogenic diet was associated with an increase in the volume of cerebellum and decreases in the volumes of hypothalamus and corpus callosum
Tay and colleagues (2008)[62]	RCT	109 adults Ages 18 to 65 Abdominal obesity and one or more metabolic syndrome risk factors	24-week diet Very Low Carbohydrate High Fat diet (VLCHF; 4% carbohydrate, 35% protein, 61% fat) High Carbohydrate Low Fat diet (HCLF; 46% carbohydrate, 24% protein, 30% fat (< 8% sat fat); <10g/d saturated fat Both diets restricted to 1430 kcal for women and 1670 kcal for men	Body weight Serum total cholesterol (TC) Serum High density lipoprotein (HDL) Serum Low density lipoprotein (LDL) Serum Triglycerides (TGs) Blood glucose C-reactive Protein (CRP)	Both diets resulted in weight loss, with no differences between groups Total cholesterol and LDL decreased in the HCLF group, but did not change in the VLCHF group HDL increased in both groups, but was higher in the VLCHF group TGs decreased in both groups, but were reduced more in the VLCHF group Fasting glucose and CRP decreased in both groups, but there were no differences between groups
Vizuete and colleagues (2013)[44]	RCT	60 male Wistar rats, 30 days old	8-week diet 3 groups: control (n=20), standard ketogenic diet (n=20), enriched omega-3 ketogenic diet (n=20) 12h light/dark cycle	BDNF concentration in hippocampi and corpus striatum	Ketogenic diet was associated with decreased BDNF content in the corpus striatum and no change in the hippocampi
Yancy and colleagues (2004)[54]	RCT	119 overweight, hyperlipidemic adults Age 18-65 y BMI 30-60 kg/m^2	Low Carbohydrate Ketogenic Diet (LCKD, < 20 g carbohydrate) (n= 59) Low Fat Diet (LFD, < 30% fat, <300mg cholesterol, 100-500 kcal restriction) (n=60) 45 LCKD and 34 LFD completed	Body weight Triglycerides (TGs) High density lipoprotein (HDL) Low density lipoprotein (LDL)	LCKD was associated with a greater decrease in body weight than the LFD TGs were decreased more in the LCKD group HDL was increased more in the LCKD group LDL was increased in both groups, but was higher in the LCKD group

Table 1. Studies investigating the ketogenic diet and characteristics of MDD

Reference	Design	Participants	Intervention	Primary Outcome(s)	Results/conclusions
Yang and colleagues (2010)[46]	RCT	Male C57BL/6 J mice 8 weeks old	2-day or 1-week diet Standard diet(SD) and water ad libitum for 1-week pre-diet Ketogenic diet or SD groups With and without 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) injections (4 injections at 2-hour intervals) Diets begin after injections	Dopamine concentrations Proinflammatory cytokine levels (Interleukin-1Beta, Interleukin-6, Tumor Necrosis Factor-alpha)	Ketogenic diet protected dopaminergic neurons against MPTP-induced degradation KD inhibited increase of proinflammatory cytokines produced by MPTP toxicity
Zhang and colleagues (2013)[40]	RCT	19 male Wistar rats, 40 days old	4-week diet: 1-week acclimation, 3-week intervention, ad libitum feeding Ketogenic diet (KD) Standard diet (SD)	Cerebral metabolic rate of glucose (CMR-glu) Blood glucose Blood lactate Blood ketones (Beta-hydroxybutyrate and acetoacetate)	No differences in plasma glucose between groups after feeding Plasma ketones higher and plasma lactate were lower in KD group than SD group CMR-glu was decreased in left and right cerebral hemispheres and cerebellum in KD group CMR-glu was lower in both hemispheres than in the cerebellum
Ziegler and colleagues (2003)[50]	RCT	20 Male Wistar rats, 30 days old	8-week diet Ketogenic diet or standard laboratory diet Food and water ad libitum	Thiobarbituric Acid Reactive Substances (TBARS) assay Total Antioxidant Reactivity (TAR) assay Catalase(CAT) assay Superoxide dismutase (SOD) assay Glutathione peroxidase (GPx) assay	TBARS levels (lipoperoxidation) was increased in cerebellum of ketogenic diet rats TAR (antioxidant capacity) was increased in hippocampus and decreased in cerebellum of ketogenic diet rats In hippocampus, CAT activity decreased ~50% and GPx activity increased ~400% in ketogenic diet rats Ketogenic diet may have neuroprotective qualities through increases in antioxidant capacity in certain regions of the brain

Manuscript References

1. Kessler RC, Bromet EJ. The Epidemiology of Depression Across Cultures. *Annu Rev Public Health*. 2013;34:119-138.

2. Weinberger AH, Gbedemah M, Martinez AM, Nash D, Galea S, Goodwin RD. Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. *Psychol Med*. 2018;48:1308-1315.

3. Read J, Sharpe L, Modini M, Dear BF. Multimorbidity and Depression: A Systematic Review and Meta-analysis. *J Affect Disord*. 2017;221:36-46.

4. Lopresti AL, Hood SD, Drummond PD. A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise. *J Affect Disord*. 2013;148:12-27.

5. Opie RS, O'Neil A, Itsiopoulos C, Jacka FN. The impact of whole-of-diet interventions on depression and anxiety: a systematic review of randomised controlled trials. *Public Health Nutr*. 2015;18:2074-2093.

6. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, D.C.: American Psychiatric Association; 2013.

7. Holthoff VA, Beuthien-Baumann B, Zündorf G, et al. Changes in brain metabolism associated with remission in unipolar major depression. *Acta Psychiatr Scand*. 2004;110:184-194.

8. Martinot JL, Hardy P, Feline A, et al. Left prefrontal glucose hypometabolism in the depressed state: a confirmation. *Am J Psychiatry*. 1990;147:1313-1317.

9. Dunn RT, Kimbrell TA, Ketter TA, et al. Principal components of the beck depression inventory and regional cerebral metabolism in unipolar and bipolar depression. *Biol Psychiatry*. 2002;51:387-399.

10. Kimbrell TA, Ketter TA, George MS, et al. Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. *Biol Psychiatry*. 2002;51:237-252.

11. Kahl KG, M.D, Georgi K, Bleich S, et al. Altered DNA methylation of glucose transporter 1 and glucose transporter 4 in patients with major depressive disorder. *J Psychiatr Res*. 2016;76:66-73.

12. Shimizu E, Hashimoto K, Okamura N, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry*. 2003;54:70-75.

13. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood–brain barrier. *Neuropharmacology*. 1998;37:1553-1561.

14. Lee B, Kim H, Park S, Kim Y. Decreased plasma BDNF level in depressive patients. *J Affect Disord*. 2006;101:239-244.

15. Sözeri-Varma G, Enli Y, Toker-Uğurlu T, Alaçam H, Kalkan-Oğuzhanoğlu N. Decreased serum BDNF levels in major depressive patients. *Neurol Psychiatry Brain Res*. 2011;17:84-88.

16. Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry J. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatry Res*. 2002;109:143-148.

17. Aydemir Ö, Deveci A, Taskin OE, Taneli F, Esen-Danaci A. Serum brain-derived neurotrophic factor level in dysthymia: A comparative study with major depressive disorder. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2007;31:1023-1026.

18. Huang T, Lee C, Liu Y. Serum brain-derived neurotrophic factor levels in patients with major depression: Effects of antidepressants. *J Psychiatr Res*. 2007;42:521-525.

19. Wolkowitz OM, Wolf J, Shelly W, et al. Serum BDNF levels before treatment predict SSRI response in depression. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2011;35:1623-1630.

20. Birkenhäger TK, Geldermans S, Van den Broek, Walter W, van Beveren N, Fekkes D. Serum brain-derived neurotrophic factor level in relation to illness severity and episode duration in patients with major depression. *J Psychiatr Res*. 2011;46:285-289.

21. Gawryluk JW, Wang J, Andreazza AC, Shao L, Young LT. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. *Int J Neuropsychopharmacol*. 2011;14:123-130.

22. Kodydková J, Vávrová L, Zeman M, et al. Antioxidative enzymes and increased oxidative stress in depressive women. *Clin Biochem*. 2009;42:1368-1374.

23. Gałecki P, Szemraj J, Bieńkiewicz M, Florkowski A, Gałecka E. Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment. *Pharmacol Rep: PR*. 2009;61:436.

24. Lindqvist D, Dhabhar FS, James SJ, et al. Oxidative stress, inflammation and treatment response in major depression. *Psychoneuroendocrinology*. 2016;76:197-205.

25. Rybka J, Kędziora-Kornatowska K, Banaś-Leżańska P, et al. Interplay between the pro-oxidant and antioxidant systems and proinflammatory cytokine levels, in relation to iron metabolism and the erythron in depression. *Free Radic Biol Med*. 2013;63:187-194.

26. Bilici M, Efe H, Köroğlu MA, Uydu HA, Bekaroğlu M, Değer O. Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. *J Affect Disord*. 2001;64:43-51.

27. Sarandol A, Sarandol E, Eker SS, Erdinc S, Vatansever E, Kirli S. Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative–antioxidative systems. *Hum Psychopharmacol: Clin Exp*. 2007;22:67-73.

28. Simon G, Von Korff M, Saunders K, et al. Association Between Obesity and Psychiatric Disorders in the US Adult Population. *Arch Gen Psychiatry*. 2006;63:824-830.

29. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes*. 2003;27:514-521.

30. Strine TW, M.P.H, Mokdad AH, Ph.D, Dube, Shanta R., Ph.D., M.P.H, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatry*. 2008;30:127-137.

31. de Wit LM, van Straten A, van Herten M, Penninx, B. W. J. H, Cuijpers P. Depression and body mass index, a u-shaped association. *BMC Public Health*. 2009;9:14.

32. Carpenter K, Hasin D, Allison D, Faith M. Relationships Between Obesity and DSM-IV Major Depressive Disorder, Suicide Ideation, and Suicide Attempts: Results From a General Population Study. *Am J Public Health*. 2000;90:251-257.

33. Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is Obesity Associated with Major Depression? Results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol*. 2003;158:1139-1147.

34. Dixon JB, Dixon ME, O'Brien PE. Depression in Association With Severe Obesity: Changes With Weight Loss. *JAMA Internl Med*. 2003;163:2058-2065.

35. Kloiber S, Ising M, Reppermund S, et al. Overweight and Obesity Affect Treatment Response in Major Depression. *Biol Psychiatry*. 2007;62:321-326.

36. Westman E, Mavropoulos J, Yancy Jr W, Volek J. A review of low-carbohydrate ketogenic diets. *Curr Atheroscler Rep*. 2003;5:476-483.

37. Freeman J, Veggiotti P, Lanzi G, Tagliabue A, Perucca E. The Ketogenic diet: from molecular mechanisms to clinical effects. *Epilepsy Res*. 2006;68:145-180.

38. Hartman AL, Gasior M, Vining EP, Rogawski MA. The Neuropharmacology of the Ketogenic Diet. *Pediatr Neurol*. 2007;36:281-292.

39. Manninen AH. Metabolic effects of the very-low-carbohydrate diets: misunderstood "villains" of human metabolism. *J Int Soc Sports Nutr*. 2004;1:7-11.

40. Zhang Y, Kuang Y, Xu K, et al. Ketosis Proportionately Spares Glucose Utilization in Brain. *J Cereb Blood Flow Metab.* 2013;33:1307-1311.

41. Bough KJ, Wetherington J, Hassel B, et al. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. *Ann Neurol*. 2006;60:223-235.

42. Genzer Y, Dadon M, Burg C, Chapnik N, Froy O. Effect of dietary fat and the circadian clock on the expression of brain-derived neurotrophic factor (BDNF). *Mol Cell Endocrinol*. 2016;430:49-55.

43. Marosi K, Kim SW, Moehl K, et al. 3-Hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. *J Neurochem*. 2016;139:769-781.

44. Vizuete AF, de Souza DF, Guerra MC, et al. Brain changes in BDNF and S100B induced by ketogenic diets in Wistar rats. *Life Sci*. 2013;92:923-928.

45. Milder JB, Liang L, Patel M. Acute oxidative stress and systemic Nrf2 activation by the ketogenic diet. *Neurobiol Dis*. 2010;40:238-244.

46. Yang X, Cheng B. Neuroprotective and Anti-inflammatory Activities of Ketogenic Diet on MPTP-induced Neurotoxicity. *J Mol Neurosci*. 2010;42:145-153.

47. Jarrett S, Milder J, Liang L, Patel M. The ketogenic diet increases mitochondrial glutathione levels. *J Neurochem*. 2008;106:1044-1051.

48. Sullivan PG, Rippy NA, Dorenbos K, Concepcion RC, Agarwal AK, Rho JM. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. *Ann Neurol*. 2004;55:576-580.

49. Greco T, Glenn TC, Hovda DA, Prins ML. Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity. *J Cereb Blood Flow Metab*. 2016;36:1603-1613.

50. Ziegler D, Ribeiro L, Hagenn M, et al. Ketogenic Diet Increases Glutathione Peroxidase Activity in Rat Hippocampus. *Neurochem Res*. 2003;28:1793-1797.

51. Murphy P, Likhodii S, Nylen K, Burnham WM. The antidepressant properties of the ketogenic diet. *Biol Psychiatry*. 2004;56:981-983.

52. Sussman D, Germann J, Henkelman M. Gestational ketogenic diet programs brain structure and susceptibility to depression & anxiety in the adult mouse offspring. *Brain Behav*. 2015;5:e00300-n/a.

53. Halyburton AK, Brinkworth GD, Wilson CJ, et al. Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. *Am J Clin Nutr*. 2007;86:580.

54. Yancy W, Olsen M, Guyton J, Bakst R, Westman E. A Low Carbohydrate, Ketogenic Diet versus a Low Fat Diet To Treat Obesity and Hyperlipidemia. *Ann Intern Med.* American College of Physicians; 2004.

55. Samaha FF, Iqbal N, Seshadri P, et al. A Low-Carbohydrate as Compared with a Low-Fat Diet in Severe Obesity. *New Engl J Med*. 2003;348:2074-2081.

56. Bazzano LA, Hu T, Reynolds K, et al. Effects of low-carbohydrate and low-fat diets: a randomized trial. *Ann Intern Med*. 2014;161:309-318.

57. Lim SS, Noakes M, Keogh JB, Clifton PM. Long-term effects of a low carbohydrate, low fat or high unsaturated fat diet compared to a no-intervention control. *Nutr Metab Cardiovasc Dis*. 2009;20:599-607.

58. Brinkworth GD, Noakes M, Buckley JD, Keogh JB, Clifton PM. Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. *Am J Clin Nutr*. 2009;90:23-32.

59. Stern L, Iqbal N, Seshadri P, Chicano K. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: One-year follow-up of a randomized trial. *ACC Curr J Rev*. 2004;13:18.

60. Noakes M, Foster PR, Keogh JB, James AP, Mamo JC, Clifton PM. Comparison of isocaloric very low carbohydrate/high saturated fat and high carbohydrate/low saturated fat diets on body composition and cardiovascular risk. *Nutr Metab* . 2006;3:7.

61. Gardner CD, Offringa LC, Hartle JC, Kapphahn K, Cherin R. Weight loss on low-fat vs. low-carbohydrate diets by insulin resistance status among overweight adults and adults with obesity: A randomized pilot trial. *Obesity*. 2016;24:79-86.

62. Tay J, Brinkworth GD, Noakes M, Keogh J, Clifton PM. Metabolic Effects of Weight Loss on a Very-Low-Carbohydrate Diet Compared With an Isocaloric High-Carbohydrate Diet in Abdominally Obese Subjects. *J Am Coll Cardiol* 2008;51:59-67.

63. Dashti HM, Mathew TC, Hussein T, et al. Long-term effects of a ketogenic diet in obese patients. *Exp Clin Cardiol*. 2004;9:200.

Appendix A

Recruitment Email

Subject: If You Are a Veteran, This Exciting Nutrition Study May Be For YOU!

Are you ready improve your overall health? Do you want a free nutrition consultation and a personalized diet plan? Do you want free body composition testing and analysis? Do you want free assessment of your blood glucose and a full lipid profile?

By participating in our study, you will have access to both a registered dietitian and fitness professional and receive a comprehensive health and nutrition assessment during the course of the study. Additionally, if you successfully complete the study, you may eligible to receive a new FitBit Charge 2.

Our names are Dr. Jeremy Akers, RDN and Jordan Murrin and we are an Associate Professor and Graduate Student research team here at James Madison University in the Health Professions Department. We are conducting a research study on the effect of two dietary interventions on body composition and metabolic health and are looking for veterans of United States Armed Forces to participate. Details of the study can be found below. If you or a friend are interested in participating, please contact Jordan Murrin via email or telephone.

Contact Information:
Name: Jordan Murrin, Graduate Student Researcher
Email: murrinja@dukes.jmu.edu
Phone: 703-565-3001

Name: Dr. Jeremy Akers, PhD, RDN
Email: akersjd@jmu.edu
Phone: 540-568-8974

Who: Any veteran of the United States Armed Forces between the ages of 18-65 years.

What: Participation includes: 12 weeks of FREE nutrition consultation; FREE tests to measure body fat and composition, blood glucose, and full lipid profiles; and a FREE personalized diet plan and dietary analysis.

When: February 2020

Thank you,
Dr. Jeremy Akers and Jordan Murrin

* Approved by the James Madison University Institutional Review Board, Protocol No. 20-1039

Sample Recruitment Flyer

JMU Nutrition Study

Be part of an important research study at James Madison University!

+ Are you a **veteran** of the United States Armed Forces?
+ Are you between **18** and **65** years of age?
+ Do you want to **change** your eating habits and **improve** your health status?

If you answered **YES** to these questions, we are excited to tell you that you may be eligible to participate in our nutrition research study.

The purpose of the 12-week research study is to compare the effectiveness of two dietary interventions on mental health, body composition and metabolic health.

Benefits include a comprehensive health and nutrition assessment with body composition, glucose, cholesterol, and **individualized** nutrition plan.

Participants will be eligible to receive a **FitBit Charge 2 watch.** *No medications will be given.*

This study is being conducted at Burruss Hall, James Madison University, 820 Madison Dr, Harrisonburg, VA 22801. Parking will be provided and you will be required to visit campus 3 times.

Please call for more information.
Jordan Murrin (*Graduate Student Researcher*) **703-565-3001**
Dr. Jeremy Akers, RD *(Primary Investigator)* **540-568-8974**

* Approved by the James Madison University Institutional Review Board, Protocol No. 20-1039
* This research is not VA research, will not be conducted by VA, has not been reviewed by VA's Institutional Review Board, and is not endorsed by VA. VA is not responsible for any costs incurred by a Veteran if the Veteran enters the study as a research subject. The announcement is being provided for information only.

Appendix B

Questionnaires

Health Status Questionnaire

1. Has anyone in your family had a heart attack, heart surgery, or sudden death due to cardiovascular disease prior to the age of 65? (Circle one) Yes No

If yes, who?

_____

How old were they? (Circle one) 54 or younger 55-59 60-64

2. Date of last medical exam: _____

3. Please list any operations that you have had:

_____

_____

_____

4. Please list any physical or mental health conditions for which you have been diagnosed or are being treated for by a physician or health professional:

_____

_____

_____

5. Please answer the questions below related to medication use:

- *If yes, please fill in the medication name.*
- *Indicate whether you have taken the medication for the given amount of time without any changes to medication type or dosage.*

Do you currently take any medications for any of the following conditions?

Depression? _____ Have you taken this for ≥ 8 weeks? _____

Anxiety? _____ Have you taken this for ≥ 8 weeks?_____

Diabetes? _____ Have you taken this for ≥ 2 weeks? _____

High cholesterol? _____ Have you taken this for ≥ 8 weeks? _____

High blood pressure? _____ Have you taken this for ≥ 2 weeks? _____

Please list all medications taken in the last six months and how long you have been taking them.

_____

_____

_____

6. The occurrence of any of these health symptoms frequently is the basis for medical attention. Please check how often you have each of the following:

Symptom	1 Rarely	2 Infrequently	3 Sometimes	4 Fairly Often	5 Very Often
Cough up blood					
Abdominal pain					
Low back pain					
Leg pain					
Arm or shoulder pain					
Chest pain					
Swollen joints					
Feel faint					
Dizziness					
Breathless on slight exertion					

7. Have you ever been diagnosed with any psychological disorders other than major depressive disorder or an anxiety disorder?

_____

If yes, please explain.

_____

8. Have you ever or do you currently use mood stabilizers or antipsychotics medications?

_____

If yes, please explain. _____

9. Have you experienced any weight loss or weight gain >10lbs (4.5 kg) in the past 6 months?

_____

If yes, please explain.

_____

10. Have you followed of a low carbohydrate diet in the past 3 months?

_____

If yes, please explain.

_____

11. Do you smoke? (Circle one) Yes No

If yes, how many per day:

Cigarettes: 1-9 10-19 20-39 40 or more

Cigars or pipes only: 5 or more or any inhaled less than 5, none inhaled

Adapted from: Howley and Franks. (1992). *Health Fitness Instructor's Handbook*. Health Status Questionnaire. Champaign: Human Kinetics.

Beck's Depression Inventory-II (BDI-II)

Please circle the answer that most accurately applies to any symptoms that you experience.

1.
- 0 I do not feel sad.
- 1 I feel sad
- 2 I am sad all the time and I can't snap out of it.
- 3 I am so sad and unhappy that I can't stand it.

2.
- 0 I am not particularly discouraged about the future.
- 1 I feel discouraged about the future.
- 2 I feel I have nothing to look forward to.
- 3 I feel the future is hopeless and that things cannot improve.

3.
- 0 I do not feel like a failure.
- 1 I feel I have failed more than the average person.
- 2 As I look back on my life, all I can see is a lot of failures.
- 3 I feel I am a complete failure as a person.

4.
- 0 I get as much satisfaction out of things as I used to.
- 1 I don't enjoy things the way I used to.
- 2 I don't get real satisfaction out of anything anymore.
- 3 I am dissatisfied or bored with everything.

5.
- 0 I don't feel particularly guilty
- 1 I feel guilty a good part of the time.
- 2 I feel quite guilty most of the time.
- 3 I feel guilty all of the time.

6.
- 0 I don't feel I am being punished.
- 1 I feel I may be punished.
- 2 I expect to be punished.
- 3 I feel I am being punished.

7.
- 0 I don't feel disappointed in myself.
- 1 I am disappointed in myself.
- 2 I am disgusted with myself.
- 3 I hate myself.

8.
- 0 I don't feel I am any worse than anybody else.
- 1 I am critical of myself for my weaknesses or mistakes.
- 2 I blame myself all the time for my faults.
- 3 I blame myself for everything bad that happens.

9.
- 0 I don't have any thoughts of killing myself.
- 1 I have thoughts of killing myself, but I would not carry them out.
- 2 I would like to kill myself.
- 3 I would kill myself if I had the chance.

10.

0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now.
3 I used to be able to cry, but now I can't cry even though I want to.

11.

0 I am no more irritated by things than I ever was.
1 I am slightly more irritated now than usual.
2 I am quite annoyed or irritated a good deal of the time.
3 I feel irritated all the time.

12.

0 I have not lost interest in other people.
1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

13.

0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions more than I used to.
3 I can't make decisions at all anymore.

14.

0 I don't feel that I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel there are permanent changes in my appearance that make me look unattractive
3 I believe that I look ugly.

15.

0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

16.

0 I can sleep as well as usual.
1 I don't sleep as well as I used to.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up several hours earlier than I used to and cannot get back to sleep.

17.

0 I don't get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

18.

0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

19.

0 I haven't lost much weight, if any, lately.
1 I have lost more than five pounds.
2 I have lost more than ten pounds.
3 I have lost more than fifteen pounds.

20.

0 I am no more worried about my health than usual.
1 I am worried about physical problems like aches, pains, upset stomach, or constipation.
2 I am very worried about physical problems and it's hard to think of much else.
3 I am so worried about my physical problems that I cannot think of anything else.

21.

0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I have almost no interest in sex.
3 I have lost interest in sex completely.

INTERPRETING THE BECK DEPRESSION INVENTORY (***For researcher use only***)

Now that you have completed the questionnaire, add up the score for each of the twenty-one questions by counting the number to the right of each question you marked. The highest possible total for the whole test would be sixty-three. This would mean you circled number three on all twenty-one questions. Since the lowest possible score for each question is zero, the lowest possible
score for the test would be zero. This would mean you circles zero on each question.

You can evaluate your depression according to the Table below.

Total Score _____	**Levels of Depression**
1-10 _____	These ups and downs are considered normal
11-16 _____	Mild mood disturbance
17-20 _____	Borderline clinical depression
21-30 _____	Moderate depression
31-40 _____	Severe depression
> 40 _____	Extreme depression

Adapted from: Beck A, Steer R, Brown G. Manual for the beck depression inventory-II. 1996.

Beck Anxiety Inventory

Below is a list of common symptoms of anxiety. Please carefully read each item in the list. Indicate how much you have been bothered by that symptom during the past month, including today, by circling the number in the corresponding space in the column next to each symptom.

	Not at All	**Mildly** – but it didn't bother me much.	**Moderately** - it wasn't pleasant at times	**Severely** – it bothered me a lot
Numbness or tingling	0	1	2	3
Feeling hot	0	1	2	3
Wobbliness in legs	0	1	2	3
Unable to relax	0	1	2	3
Fear of worst happening	0	1	2	3
Dizzy or lightheaded	0	1	2	3
Heart pounding/racing	0	1	2	3
Unsteady	0	1	2	3
Terrified or afraid	0	1	2	3
Nervous	0	1	2	3
Feeling of choking	0	1	2	3
Hands trembling	0	1	2	3
Shaky/unsteady	0	1	2	3
Fear of losing control	0	1	2	3
Difficulty in breathing	0	1	2	3
Fear of dying	0	1	2	3
Scared	0	1	2	3
Indigestion	0	1	2	3
Faint/lightheaded	0	1	2	3
Face flushed	0	1	2	3
Hot/cold sweats	0	1	2	3

For researcher use only

Column Sum				

Scoring - Sum each column. Then sum the column totals to achieve a total score. Write that score below.

Total Sum _____

Interpretation

A grand sum between **0 – 21** indicates very low anxiety. That is usually a good thing. However, it is possible that you might be unrealistic in either your assessment which would be denial or that you have learned to "mask" the symptoms commonly associated with anxiety. Too little "anxiety" could indicate that you are detached from yourself, others, or your environment.

A grand sum between **22 – 35** indicates moderate anxiety. Your body is trying to tell you something. Look for patterns as to when and why you experience the symptoms described above. For example, if it occurs prior to public speaking and your job requires a lot of presentations you may want to find ways to calm yourself before speaking or let others do some of the presentations. You may have some conflict issues that need to be resolved. Clearly, it is not "panic" time, but you want to find ways to manage the stress you feel.

A grand sum that **exceeds 36** is a potential cause for concern. Again, look for patterns or times when you tend to feel the symptoms you have circled. Persistent and high anxiety is not a sign of personal weakness or failure. It is, however, something that needs to be proactively treated or there could be significant impacts to you mentally and physically. You may want to consult a counselor if the feelings persist.

Adapted from: Beck AT, Epstein N, Brown G, Steer RA. An inventory for measuring clinical anxiety. *Journal of Consulting and Clinical Psychology*. 1988;56(6):893-897.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No → ***Skip to PART 2: TRANSPORTATION***

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related physical activity → ***Skip to question 4***

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related physical activity → ***Skip to question 6***

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**
_____ **minutes per day**

6. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → ***Skip to PART 2: TRANSPORTATION***

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**
_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

_____ **days per week**

☐ No traveling in a motor vehicle → ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**
_____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No bicycling from place to place → ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**
_____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**
_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → ***Skip to question 18***

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**
_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home → ***Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY***

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**
_____ **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → ***Skip to question 22***

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day** _____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → ***Skip to question 24***

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day** _____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → ***Skip to PART 5: TIME SPENT SITTING***

25. How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day** _____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day** _____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day** _____ **minutes per day**

Adapted from: Booth M. Assessment of physical activity: An International perspective. Research Quarterly for Exercise and Sport. 2000;71:114–120.

Appendix C

Ketogenic Diet Handout

Participant ID #: _____

Welcome to our research study and thank you for your participation! If you have any questions or concerns at any time during your participation, please contact our research team.

Graduate Student Researcher
Jordan Murrin
murrinja@dukes.jmu.edu
703-565-3001

Research Supervisor
Jeremy Akers, PhD, RDN
akersjd@jmu.edu
540-568-8974

Appendix A – Ketogenic Diet

The ketogenic diet is a dietary plan that is high in fat and very low in carbohydrates, while maintaining adequate protein intake. It requires a restriction of carbohydrate intake to achieve "ketosis", which mimics a fasted state and forces the body to utilize fats from your diet and those stored in your body for fuel. As these fats are broken down for energy, they are turned into ***ketones***, which replace most of your body's carbohydrates as a major source for energy.

To benefit from the ketogenic diet, it is important to eat foods that are low in carbohydrates and to eat the appropriate number of calories to achieve and maintain a healthy weight. The diet typically includes plenty of fatty fish, meats, eggs, nuts, seeds, vegetable-based oils, and fibrous vegetables.

This handout is meant to provide you with recommendations that you may use to maintain the ketogenic diet. The main goal for the ketogenic diet is to achieve ketosis by restricting your total carbohydrate intake to **less than 50 grams of carbohydrates per day**. You can accomplish this by reading nutrition labels on food, planning your meals, and even using the provided resources to make "keto-friendly" recipes.

The tables on the next page outlines the main food groups and provides instructions for making food choices that are higher in fat and lower in carbohydrate. An emphasis on foods high in saturated fat is not recommended by the Dietary Guidelines for Americans and the American Heart Association and may have adverse effects on blood LDL cholesterol. Therefore, for this diet, you should emphasize high-total fat foods that are also lower in saturated fat such as **fatty fish, avocado, nuts, seeds, and vegetable-based oils (includes canola, corn, olive, peanut, safflower, sesame, soybean, and sunflower oils).**

Approximate Daily Calorie Needs for Men

Age (years)	Calories Needed for Sedentary Activity Level	Calories Needed for Moderately Active Activity Level	Calories Needed for Active Activity Level
19–30	2,400 – 2,600	2,600–2,800	3,000
31–50	2,200-2,400	2,400–2,600	2,800–3,000
51+	2,000-2,200	2,200–2,400	2,400–2,800

Approximate Daily Calorie Needs for Women

Age (years)	Calories Needed for Sedentary Activity Level	Calories Needed for Moderately Active Activity Level	Calories Needed for Active Activity Level
19–30	1,800-2,000	2,000-2,200	2,400
31–50	1,800	2,000	2,200
51+	1,600	1,800	2,200

Tips for Eating Out on Keto

- **Avoid starches**
  - Ask for your food to be served without bread, pasta, potatoes, or rice
  - Be wary of starchy vegetables like potatoes (all types/forms), corn, peas, beets, carrots, or onions
  - See the "Low Carbohydrate Foods and Foods to Avoid" handout to determine what foods should be avoided
- **Add healthy fat**
  - Ask for extra butter for veggies or meat
  - Use olive oil and vinegar dressing
  - Use heavy cream or coconut milk in your coffee or tea
- **Watch out for sauces and condiments**
  - Some contain mostly fat, but others have added sugars
- **Choose the appropriate drink**
  - Plain water, sparkling water (no sugar added), tea, or coffee are great options
  - Avoid sugar-sweetened beverages, juices, and alcohol
- **Rethink dessert**
  - Most dessert are not only high in fat, but added sugars too
  - Drink (decaf) coffee or tea with cream or coconut milk instead

Appendix B - Low Carbohydrate Foods and Foods to Avoid

This handout is meant to give you a better idea of what foods to choose in order to maintain your low-carbohydrate diet. It will give you general DOs and DON'Ts in terms of food choices so that you have a general idea of some low-carb and high-carb foods. The first column will consist of your low-carb foods, while the "avoid" column will consist of high-carb foods that you will want to avoid and eliminate from your diet. Keep in mind that this list is not exhaustive and there other low-carb foods that are not on this list.

Experimenting and combining low-carb foods in different ways will keep your diet from becoming monotonous. Meal prepping in advance may be beneficial if you have limited time during the week to cook meals so that you always have food ready to eat. Having meals and snacks ready in advance may also prevent any temptation or impulse to eat high-carb foods that are not permitted while following this regiment.

It is important to pay attention to what you eat because some of these foods do contain carbohydrates. If you over-consume a particular food, you may easily go over your daily 50 g CHO limit. Yogurt and cottage cheese especially should be consumed in moderation.

	Zero/Low CHO foods		**Avoid**
Meats, Fish, & Alternatives	Steak Ground hamburger Bacon* Sausage* Pork Ham* Salmon Cod Flounder Lamb Tofu* Prepackaged lunch meats	Chicken (skin on) Eggs Veal Venison Duck Tuna* Shellfish Tilapia Shrimp Lobster (all un-breaded meat)	Any breaded meats or fish Look for additives in canned tuna Tempeh Seitan
Dairy Products & Alternatives	Cottage cheese (1/2 c) Brie (1 oz) Camembert (1 oz) Blue cheese (1 oz) Cheddar (1 oz) Sheep and goat cheeses (1 oz) Mozzarella (1 oz)	Whole milk (<1c/day) High-fat yogurts (plain only) Cream (40% fat or more) Sour cream Almond milk (unsweetened) Coconut milk (unsweetened) Feta (1 oz)	Ice cream Yogurts with added fruit Low fat dairy Milk
Oils, Fats, & Nuts/Seeds	Peanut butter (no added sugar) Almond butter (no added sugar)	Butter Canola oil Vegetable oil Almonds Shortening	Margarine

	Sunflower butter (no added sugar) Olive oil Coconut oil Mayonnaise*	Sesame oil Sunflower seeds Pine nuts Peanuts Walnuts Macadamia nuts Pumpkin seeds Pecans	
Vegetables	Cabbage Broccoli Brussel sprouts Kale Spinach Celery Bok choy Bell pepper Alfalfa sprouts Chives Endive Fennel Radicchio Artichoke hearts	Avocado (1/2 whole) Eggplant Asparagus Zucchini Cucumber Swiss chard Tomatoes Radishes Chicory greens Daikon Mushrooms Iceberg/Romaine Olives	Potatoes (all types/forms) Corn Peas Parsnips Plantains Beets Carrots Onions
Fruits	No fruit allowed		Avoid all fruit
Grains	No grains allowed		Avoid all breads, pastas, wheat, spelt, rye, barley, cereals
Herbs/Spices	Basil Dill Garlic Oregano Rosemary Tarragon Cinnamon Nutmeg Paprika	Cayenne pepper Cilantro Ginger Pepper Sage Turmeric Curry Thyme Salt	Spice mixtures may contain added sugar

Salad Dressings	Balsamic vinegar Caesar (2 tbs) Italian (2 tbs)	Oil and vinegar (2 tbs) Blue cheese (2 tbs) Ranch (2 tbs)	No dressings with added sugar and no more than 2 grams of net carbs per serving
Beverages	Clear broth* Flavored seltzer* Water	Carbonated water Decaf coffee or tea Diet soda	Beer/wine/liquor** Gatorade Endurance/energy drinks Regular soda Fruit beverages Chocolate milk
Other	Mustard* Soy sauce Horseradish Salsa* Pesto* Cider/wine vinegars Teriyaki sauce		Artificial sweeteners Jams, jellies, preserves Chips, pretzels Cookies, cakes, candy Ketchup, Tartar sauce Steak sauce Barbeque sauce
***Check all labels for added sugars or fillers that may add carbs**			

****Alcoholic beverages should be minimized, as alcohol reduces ketosis****

However, there are some low carbohydrate beers available, such as Michelob Ultra (2.6g carbs), Corona Premier (2.6g carbs), and Miller Lite (3.2g carbs).

DO NOT UTILIZE ANY EXOGENOUS KETO SUPPLEMENTS

Includes ketone salts, ketone esters, and β-hydroxybutyrate (βHB)

Appendix C - Sample Menus

Sample Menu 1

Breakfast (534 kcal, 6g carbs)

Omelet

3 eggs	214 kcal, 1g carbs
1.5 tbsp of butter	152 kcal
¼ cup cheddar cheese	114 kcal
½ avocado	109 kcal, 5g carbs

Snack (149 kcal, 12g carbs)

8 ounces of whole milk	149kcal, 12g carbs

Lunch (657 kcal, 1g carbs)

6 oz 80% lean hamburger patty, no bun	470kcal
1 slice of provolone cheese	100kcal, 1g carbs
2 medium slices of bacon	87kcal

Snack (204 kcal, 11g carbs)

1 cup of celery	16 kcal, 3g carbs
2 tbsp. of peanut butter	188kcal, 8g carbs

Dinner (662 kcal, 6g carbs)

6-ounce chicken leg quarter, skin eaten	392kcal
1 cup of broccoli	30kcal, 6g carbs
2 tbsp. of canola oil	240kcal

Totals: 2,206 kcal, 36g carbs, 6.5% carbs

Sample Menu 2

Breakfast (379 kcal, 12g carbs)

2 medium slices of bacon	87 kcal
2 large hard-boiled eggs	154kcal, 1g carbs
8 ounces full fat plain yogurt	138kcal, 11g carbs

Snack (171 kcal, 2g carbs)

2 ounces of mozzarella cheese (2 slices or 2 cheese sticks)	171kcal, 2g carbs

Lunch (611 kcal, 7g carbs)

6-ounce pork chop	405kcal
1 cup of cottage cheese	206kcal, 7g carbs

Snack (321 kcal, 17g carbs)

8 ounces of whole milk	149kcal, 12g carbs
1 ounce of almonds (22 almonds)	172kcal, 5g carbs

Dinner (756 kcal, 4g carbs)

6-ounce steak, fat eaten	404kcal
2 cups of raw spinach	14kcal, 2g carbs
¼ cup of feta cheese	99 kcal, 2g carbs
2 tbsp. of olive oil	239kcal

Totals: 2,238 kcal, 42g carbs, 7.5% carbs

Appendix D - Meal Planning Resources

Recipe Resources

1. https://www.dietdoctor.com/low-carb/keto/recipes
2. https://www.tasteofhome.com/collection/keto-diet-recipes/view-all/
3. https://www.delish.com/keto-recipes/
4. https://www.allrecipes.com/recipes/22959/healthy-recipes/keto-diet/
5. https://www.ditchthecarbs.com/recipes/

Sample Recipes

Breakfast

1) Baked Eggs with Coconut Milk and Cilantro

a) Ingredients
   i) Virgin coconut or vegetable oil (for ramekins)
   ii) 2 large eggs
   iii) 2 tablespoons unsweetened coconut milk
   iv) Kosher salt
   v) ½ cup cilantro leaves with tender stems
   vi) 1 teaspoon fresh lime juice
   vii) 1 teaspoon green hot sauce
   viii) Store-bought fried shallots (for serving)

b) Instructions
   i) Preheat oven to 300°. Coat 2 small ramekins or other ovenproof dishes with oil. Add 1 large egg and 1 Tbsp. coconut milk to each. Set on a rimmed baking sheet and bake until eggs are barely set, 11–14 minutes; season with salt.
   ii) Toss cilantro in a small bowl with lime juice and hot sauce; season with salt. Top eggs with cilantro mixture and shallots.

2) Keto Pancakes

a) Ingredients
   i) 2 cups almond flour
   ii) 8 tbsp butter, melted
   iii) 1 tbsp avocado oil (or coconut)
   iv) 1/4 cup water
   v) 4 eggs
   vi) 1 tsp vanilla extract

vii) 1 tsp baking powder
viii) 2 tbsp sweetener of choice
ix) pinch of salt
x) extra butter for griddle

b) Instructions
i) Combine all ingredients in blender or food processor. Let mix until fully combined. Let batter rest 5 minutes before cooking.
ii) Set a griddle (or nonstick skillet) to MED LOW heat. Use a 1/3 cup measuring cup to portion out pancake batter.
iii) Cook until edges are firming up. The pancakes will not bubble up like traditional ones but there will be little bubbles.
iv) Flip and cook 1 additional minute.
v) Serve hot with a pat of butter and sugar free maple syrup

3) **Frittata with spinach**
a) Ingredients
i) 5 oz. diced bacon or chorizo
ii) 2 tbsp butter
iii) 8 oz. fresh spinach
iv) 8 eggs
v) 1 cup heavy whipping cream
vi) 5 oz. shredded cheese
vii) salt and pepper

b) Instructions
i) Preheat the oven to 350°F (175°C). Grease a 9x9 baking dish or individual ramekins.
ii) Fry the bacon in butter on medium heat until crispy. Add the spinach and stir until wilted. Remove the pan from the heat and set aside.
iii) Whisk the eggs and cream together and pour into baking dish or in ramekins.
iv) Add the bacon, spinach and cheese on top and place in the middle of the oven. Bake for 25–30 minutes or until set in the middle and golden brown on top.

Lunch/Dinner

1) **Keto Chicken Enchilada Bowl**
a) Ingredients
i) 2 tablespoons coconut oil (for searing chicken)
ii) 1 pound of boneless, skinless chicken thighs
iii) 3/4 cup red enchilada sauce
iv) 1/4 cup water
v) 1/4 cup chopped onion
vi) 1– 4 oz can diced green chilis
vii) toppings (feel free to customize)

(1) 1 whole avocado, diced
(2) 1 cup shredded cheese (I used mild cheddar)
(3) 1/4 cup chopped pickled jalapenos
(4) 1/2 cup sour cream
(5) 1 roma tomato, chopped

viii) **Optional:** serve over plain cauliflower rice for a more complete meal!

b) Instructions
i) In a pot or dutch oven over medium heat melt the coconut oil. Once hot, sear chicken thighs until lightly brown.
ii) Pour in enchilada sauce and water then add onion and green chilis. Reduce heat to a simmer and cover. Cook chicken for 17-25 minutes or until chicken is tender and fully cooked through to at least 165 degrees internal temperature.
iii) Carefully remove the chicken and place onto a work surface. Chop or shred chicken (your preference) then add it back into the pot. Let the chicken simmer uncovered for an additional 10 minutes to absorb flavor and allow the sauce to reduce a little.
iv) To Serve, top with avocado, cheese, jalapeno, sour cream, tomato, and any other desired toppings. Feel free to customize these to your preference. Serve alone or over cauliflower rice if desired just be sure to update your personal nutrition info as needed.

2) Lemon Butter Fish

a) Ingredients
i) LEMON BUTTER SAUCE**:**
(1) 60 g / 4 tbsp unsalted butter, *cut into pieces*
(2) 1 tbsp fresh lemon juice
(3) Salt and finely ground pepper

ii) CRISPY PAN-FRIED FISH:
(1) 2 x thin white fish fillets (120-150g / 4-5oz each), skinless boneless (I used Bream, Note 1)
(2) Salt and pepper
(3) 2 tbsp white flour
(4) 2 tbsp oil

iii) SERVING:
(1) Lemon wedges
(2) Finely chopped parsley, optional

b) Instructions
i) LEMON BUTTER SAUCE:
(1) Place the butter in a light-colored saucepan or small skillet over medium heat.

(2) Melt butter then leave on the stove, whisking / stirring every now and then. When the butter turns golden brown and it smells nutty - about 3 minutes, remove from stove immediately and pour into small bowl. (Note 2)
(3) Add lemon juice and a pinch of salt and pepper. Stir then taste when it has cooled slightly. Adjust lemon/salt to taste.
(4) Set aside - it will stay pourable for 20 - 30 minutes. See Note 3 for storing.

ii) CRISPY PAN-FRIED FISH:
(1) Pat fish dry using paper towels. Sprinkle with salt & pepper, then flour. Use fingers to spread flour. Turn and repeat. Shake excess flour off well, slapping between hands if necessary.
(2) Heat oil in a non-stick skillet over high heat. When the oil is shimmering and there are faint wisps of smoke, add fish. Cook for 1 1/2 minutes until golden and crispy on the edges, then turn and cook the other side for 1 1/2 minutes (cook longer if you have thicker fillets).
(3) Remove immediately onto serving plates. Drizzle each with about 1 tbsp of Sauce (avoid dark specks settled at the bottom of the bowl), garnish with parsley and serve with lemon on the side.

3) Caveman Chili

a) Ingredients
i) 2 pounds ground pork
ii) 8 thick slices bacon, chopped
iii) 1 (14.5 ounce) can diced tomatoes, drained
iv) 1 onion, chopped
v) 3 small green bell peppers, chopped
vi) 1 (6 ounce) can tomato paste
vii) 1 (1.25 ounce) package chili seasoning (such as McCormick®)
viii) 1 pinch garlic powder, or more to taste
ix) 1 pinch onion powder, or more to taste
x) salt and ground black pepper to taste
xi) 1 pinch ground cayenne pepper, or more to taste

b) Instructions
i) Place pork in a skillet over medium heat; season with salt and pepper. Cook and stir until browned and crumbly, 5 to 7 minutes. Drain and discard grease. Transfer pork to a slow cooker.
ii) Place bacon in the hot skillet and cook over medium-high heat until evenly browned, about 10 minutes. Drain and discard grease. Transfer bacon to the slow cooker.

iii) Combine drained tomatoes, onion, green bell pepper, and tomato paste into the slow cooker. Add seasoning packet, garlic powder, onion powder, and salt, pepper, cayenne pepper; stir to combine.
iv) Cook on Low until flavors have combined, about 6 hours.

Snacks

1) Bacon Blue Cheese Deviled Eggs

a) Ingredients
   i) 8 hard-boiled eggs
   ii) ¼ cup sour cream
   iii) 1/3 cup mayonnaise
   iv) 1 Tablespoon Dijon mustard
   v) ½ teaspoon kosher salt
   vi) ¼ teaspoon pepper
   vii) ¼ teaspoon dill
   viii) ¼ cup crumbled blue cheese
   ix) 3 slices of cooked bacon chopped fine
   x) Parsley for garnish
b) Instructions
   i) To boil the perfect egg, simply place raw eggs in cold water and bring to a boil. Once your reach a boil, set a timer for 10 minutes. When time is up, drain and rinse the eggs in cold water and peel as soon as they are cool enough to handle.
   ii) Cut each hard-boiled egg in half and place the cooked yolk into a bowl and the cooked egg white onto an egg plate.
   iii) With a fork, mash the egg yolks until they resemble coarse crumbs. Add in the sour cream, mayo, mustard and salt and pepper and mix very well until the mixture is creamy (you could do this in a food processor if you wanted). Stir in the remaining ingredients and taste the filling for seasoning. If the filling seems a little dry, add in a spoonful more mayo

2) Keto Fat Bombs

a) Ingredients
   i) 2 tablespoons coconut oil
   ii) 2 tablespoons cocoa powder unsweetened
   iii) 1/2 cup natural peanut butter
   iv) 1/4 cup chia seeds
   v) 1 teaspoon vanilla essence
   vi) 2 tablespoons xylitol (or your preferred sweetener)
   vii) 1/3 cup unsweetened shredded coconut
b) Instructions

i) Melt Coconut Oil
ii) Put all ingredients "except melted coconut oil and shredded coconut" into a bowl and mix well.
iii) Add melted coconut oil and mix until combined. Place the mixture in the fridge for 30 minutes to allow the chia seeds to soak up the excess liquid and the coconut oil to set.
iv) Spread shredded coconut out onto a flat dinner plate or tray.
v) Take one heaped tablespoon of the mix and roll it into a ball in the palm of your hand.
vi) Roll the fat bomb around in the shredded coconut until coated and place on a tray lined with baking paper.
vii) When all of the mix has been rolled into fat bombs, place the tray in the refrigerator for 1 hour, or until the balls have firmed up.
viii) When the fat bombs are firm, they're ready to eat. Keep them in the fridge (particularly if you live in hot climates), they will keep for a week.

3) Buffalo Chicken Sausage Balls

a) Ingredients
i) Sausage Balls:
(1) 2 14- ounce packages al fresco fresh Buffalo-Style chicken sausage casings removed
(2) 2 cups almond flour
(3) 1 ½ cups shredded cheddar cheese
(4) ½ cup crumbled blue cheese optional
(5) 1 tsp salt
(6) ½ tsp pepper
ii) Blue Cheese Ranch Dipping Sauce:
(1) 1/3 cup mayonnaise
(2) 1/3 cup unsweetened almond milk can substitute regular milk
(3) 2 cloves garlic minced
(4) 1 tsp dried dill
(5) ½ tsp dried parsley
(6) ½ tsp salt
(7) ½ tsp pepper
(8) ¼ cup crumbled blue cheese or more, if desired

b) Instructions
i) Sausage Balls:
(1) Preheat oven to 350F and line two large baking sheets with parchment paper or tin foil.
(2) In a large bowl, combine sausage, almond flour, cheddar cheese, bleu cheese, salt and pepper. Mix thoroughly until well combined.

(3) Roll into 1-inch balls and place about an inch apart on prepared baking sheets. Bake 25 minutes, until golden brown. Serve warm with dipping sauce.

ii) Dipping Sauce:

(1) While sausage balls are baking, combine mayonnaise, almond milk, garlic, dill, parsley, salt, and pepper in a medium bowl. Stir well and then mix in crumbled blue cheese.

Appendix E - Dietary Compliance Checklist

You have been randomized to the Ketogenic diet group. For more details on your assigned diet, please see handout titled "Low Carbohydrate Foods and Foods to Avoid". This checklist can be used to ensure compliance with your ketogenic diet, by tracking intake of these items for your reference when completing your online weekly check-in survey. During the weekly check-in, you will be asked to indicate if you consumed any of the foods listed here, and provide the food item and how much of you consumed.

Day	Food Groups (circle all that apply)	Item	Quantity
Monday	**Fruit (fresh, dried, or frozen)** **Starchy vegetables** **Beans** **Pasta** **Breads (bagels, toast, buns, English muffins)** **Cereal (hot or cold)** **Candy, Cookies, Cakes, Chips** **Sports drinks/ Sugary drinks** **Milk/dairy/alternatives**		
Tuesday	**Fruit (fresh, dried, or frozen)** **Starchy vegetables** **Beans** **Pasta** **Breads (bagels, toast, buns, English muffins)** **Cereal (hot or cold)** **Candy, Cookies, Cakes, Chips** **Sports drinks/ Sugary drinks** **Alcohol** **Milk/dairy/alternatives**		

Wednesday	**Fruit (fresh, dried, or frozen)** **Starchy vegetables** **Beans** **Pasta** **Breads (bagels, toast, buns, English muffins)** **Cereal (hot or cold)** **Candy, Cookies, Cakes, Chips** **Sports drinks/ Sugary drinks** **Alcohol** **Milk/dairy/alternatives**		
Thursday	**Fruit (fresh, dried, or frozen)** **Starchy vegetables** **Beans** **Pasta** **Breads (bagels, toast, buns, English muffins)** **Cereal (hot or cold)** **Candy, Cookies, Cakes, Chips** **Sports drinks/ Sugary drinks** **Alcohol** **Milk/dairy/alternatives**		

Friday	**Fruit (fresh, dried, or frozen)** **Starchy vegetables** **Beans** **Pasta** **Breads (bagels, toast, buns, English muffins)** **Cereal (hot or cold)** **Candy, Cookies, Cakes, Chips** **Sports drinks/ Sugary drinks** **Alcohol** **Milk/dairy/alternatives**		
Saturday	**Fruit (fresh, dried, or frozen)** **Starchy vegetables** **Beans** **Pasta** **Breads (bagels, toast, buns, English muffins)** **Cereal (hot or cold)** **Candy, Cookies, Cakes, Chips** **Sports drinks/ Sugary drinks** **Alcohol** **Milk/dairy/alternatives**		

Sunday	**Fruit (fresh, dried, or frozen)** **Starchy vegetables** **Beans** **Pasta** **Breads (bagels, toast, buns, English muffins)** **Cereal (hot or cold)** **Candy, Cookies, Cakes, Chips** **Sports drinks/ Sugary drinks** **Alcohol** **Milk/dairy/alternatives**		

Appendix F – Urinary Ketone Daily Record

You have been randomized to the Ketogenic diet group. This record is designed to assess your compliance with your assigned diet by measuring ketones in your urine. **You will test your urine each morning before having anything to eat or drink** (except plain water)**.** Drinking plain water is encouraged to ensure that you are hydrated and can produce the required urinary sample. You will report these results to your researcher each week along with your Dietary Compliance Checklist during your online weekly check-in survey.

To test your urinary ketones, follow these steps:

1) Collect a small sample of your urine in one of the provided cups.
2) Place the end of the ketone testing strip in the urine sample and let it to sit for the specified time listed in the instructions on the testing strips bottle.
3) After this time has passed, remove the testing strip from the urine sample and compare the color of the testing strip to the provided chart on the testing strips bottle.
4) Use the matching color to determine whether your sample was a positive or negative for ketones.
5) Indicate your daily result in the chart – write "+" for a positive test result and "–" for a negative test result.

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Week 0							
Week 1							
Week 2							
Week 3							
Week 4							
Week 5							
Week 6							
Week 7							
Week 8							
Week 9							
Week 10							
Week 11							
Week 12							
Week 13							

Food Intake Record

Day 1 2 3 4 Date: ______________

Circle one option

Meal (breakfast, lunch, dinner, snack)	**Time**	**Meal Location (restaurant, home, work, etc.)**	**Name of Food Item or Beverage (provide as much detail as possible, *one food item per line)***	**Amount consumed (cups, tsp., Tbsp., ounces, etc.)**

DASH Diet Handout

Participant ID #: _____

Welcome to our research study and thank you for your participation! If you have any questions or concerns at any time during your participation, please contact our research team.

Graduate Student Researcher
Jordan Murrin
murrinja@dukes.jmu.edu
703-565-3001

Research Supervisor
Jeremy Akers, PhD, RDN
akersjd@jmu.edu
540-568-8974

Appendix A – DASH Diet

Dietary Approaches to Stop Hypertension (DASH) is a balanced eating plan that promotes life-long heart-healthy dietary patterns. It does not require any specific foods, but instead recommends: 1) eating a wide variety of vegetables, fruits, and whole grains; 2) moderating consumption of fat-free or low-fat dairy products, fish, poultry, beans, nuts, and vegetable oils; and 3) limiting foods that are high in saturated fat, such as fatty meats, full-fat dairy products, and tropical oils such as coconut, palm kernel, and palm oils.

To benefit from DASH, it is important to eat the appropriate number of calories to achieve and maintain a healthy weight. You can accomplish this by reading nutrition labels on food, planning your meals, and even using the provided resources to make heart-healthy recipes.

This handout is meant to provide you with recommendations that you may use to maintain the DASH diet. The tables on the next page outlines the main food groups and provides the approximate number of daily servings, different amounts of foods that equal one serving size, and examples of nutritious foods for each group. By following these recommendations, your diet will be: lower in saturated and *trans* fats; higher in potassium, calcium, magnesium, fiber, and protein; and lower in sodium. Additional tips for lowering your intake of sodium/salt are provided below.

Approximate Daily Calorie Needs for Men

Age (years)	Calories Needed for Sedentary Activity Level	Calories Needed for Moderately Active Activity Level	Calories Needed for Active Activity Level
19–30	2,400	2,600–2,800	3,000
31–50	2,200	2,400–2,600	2,800–3,000
51+	2,000	2,200–2,400	2,400–2,800

Approximate Daily Calorie Needs for Women

Age (years)	Calories Needed for Sedentary Activity Level	Calories Needed for Moderately Active Activity Level	Calories Needed for Active Activity Level
19–30	1,800-2,000	2,000-2,200	2,400
31–50	1,800	2,000	2,200
51+	1,600	1,800	2,200

Ways to Control Calories

The DASH eating plan can be used to help you lose weight. To lose weight, follow the DASH eating plan and try to reduce your total daily calories gradually. Find out your daily calorie needs or goals using a Body Weight Planner and calorie chart.

General tips for reducing daily calories include:

- Eat smaller portions more frequently throughout the day.
- Reduce the amount of meat that you eat while increasing the amount of fruits, vegetables, whole grains, or dry beans.
- Substitute low-calorie foods, such as when snacking (choose fruits or vegetables instead of sweets and desserts) or drinking (choose water instead of soda or juice), when possible.

Increasing Daily Potassium

The DASH eating plan is designed to be rich in potassium, with a target of 4,700 mg potassium daily, to enhance the effects of reducing sodium on blood pressure. The following are examples of potassium-rich foods.

Food	Potassium (mg)	Food	Potassium (mg)
Potato, 1 small	738	Prunes, stewed, ½ cup	398
Plain yogurt, nonfat or low-fat, 8 ounces	530–570	Skim milk, 1 cup	382
Sweet potato, 1 medium	542	Apricots, ¼ cup	378
Orange juice, fresh, 1 cup	496	Pinto beans, cooked, ½ cup	373
Lima beans, ½ cup	478	Pork tenderloin, 3 ounces	371
Soybeans, cooked, ½ cup	443	Lentils, cooked, ½ cup	365
Banana, 1 medium	422	Kidney beans, cooked, ½ cup	360
Fish (cod, halibut, rockfish, trout, tuna), 3 ounces	200–400	Split peas, cooked, ½ cup	360
Tomato sauce, ½ cup	405	Almonds, roasted, ⅓ cup	310

Tips for Lowering Sodium When Shopping, Cooking, and Eating Out

- Shopping
    - Choose items that are lower in sodium and salt, particularly frozen or prepackaged convenience foods and condiments.
    - Choose fresh lean meats, poultry, and fish instead of cured food such as bacon and ham.
    - Choose fresh or frozen versus canned fruits and vegetables.
    - Avoid food with added salt, such as pickles, pickled vegetables, olives, and sauerkraut.
    - Avoid instant or flavored rice and pasta.
- Cooking
    - Don't add salt when cooking rice, pasta, and hot cereals.
    - Flavor your foods with salt-free seasoning blends, fresh or dried herbs and spices, or fresh lemon or lime juice.
    - Rinse canned foods or foods soaked in brine to remove the sodium.
    - Use less table salt to flavor food.
- Eating Out
    - Ask that foods be prepared without added salt.
    - Avoid choosing menu items that have salty ingredients such as bacon, pickles, olives, and cheese or that include foods that are pickled, cured, smoked, or made with soy sauce or broth.
    - Choose fruit or vegetables as a side dish, instead of chips or fries.

DASH Daily Eating Plan for 2000 Calories			
Food Groups	**Servings per day**	**Equivalent Serving Size**	**Examples and Notes**
Grains[a]	6 – 8	1 slice bread 1 cup ready-to-eat cereal[b] ½ cup cooked rice, pasta, or cereal[b]	Whole-wheat bread and rolls, whole-wheat pasta, English muffin, pita bread, bagel, cereals, grits, oatmeal, brown rice, unsalted pretzels and popcorn
Lean meats, poultry, and fish	6 or less	1-ounce cooked lean meat, skinless poultry, or fish 1 egg	Select only lean; trim away visible fats; broil, roast, or poach; remove skin from poultry
Vegetables	4 – 5	1 cup raw leafy vegetable ½ cup cooked vegetable 6 ounces vegetable juice	Broccoli, carrots, collards, green beans, green peas, kale, lima beans, potatoes, spinach, squash, sweet potatoes, tomatoes
Fruits	4 – 5	1 medium fruit ¼ cup dried fruit ½ cup fresh, frozen, or canned fruit 6 ounces 100% fruit juice	Apples, apricots, bananas, dates, grapes, oranges, grapefruit, grapefruit juice, mangoes, melons, peaches, pineapples, raisins, strawberries, tangerines
Low-fat or fat-free dairy products[c]	2 – 3	8 ounces 1% or skim milk 1 cup low-fat or nonfat yogurt 1½ ounces part-skim cheese	Fat-free milk or buttermilk; fat-free, low-fat, or reduced-fat cheese; fat-free/low-fat regular or frozen yogurt
Fats and oils[d]	2 – 3	1 teaspoon soft margarine 1 tablespoon low-fat mayonnaise 2 tablespoons light salad dressing 1 teaspoon vegetable oil	Soft margarine, vegetable oil (canola, corn, olive, safflower), low-fat mayonnaise, light salad dressing
Nuts, seeds, and legumes (dry beans)	4 – 5 per week	1/3 cup or 1½ ounces nuts 2 tablespoon nut butter 2 tablespoon or ½ ounce seeds ½ cup cooked dry beans	Almonds, filberts, mixed nuts, peanuts, walnuts, sunflower seeds, peanut butter, kidney beans, lentils, split peas
Sweets and added sugars	5 per week	1 tablespoon sugar 1 tablespoon jelly or jam ½ ounce jelly beans 8 ounces lemonade	Fruit-flavored gelatin, fruit punch, hard candy, jelly, maple syrup, sorbet and ices, sugar
Sodium[e]	≤ 2,300 mg	Low sodium: ≤ 140 mg* Very low: ≤ 35 mg* Sodium free: ≤ 5 mg*	*mg of sodium per serving
Water	~ 3.7 L (125 fl oz)	—	—

[a] Whole grains are recommended for most grain servings as a good source of fiber and nutrients.

[b] Serving sizes vary between ½ cup and 1¼ cups, depending on cereal type. Check the product's Nutrition Facts label.

[c] For lactose intolerance, try either lactase enzyme pills with dairy products or lactose-free or lactose-reduced milk.

[d] Fat content changes the serving amount for fats and oils. For example, 1 Tbsp regular salad dressing = one serving; 1 Tbsp low-fat dressing = one-half serving; 1 Tbsp fat-free dressing = zero servings.

[e] The DASH eating plan has a sodium limit of either 2,300 mg or 1,500 mg per day. 1,500 mg of daily sodium lowers blood pressure more than 2,300 mg daily sodium.

Adapted from the National Heart, Lung, and Blood Institute (http:/www.nhlbi.nih.gov/health/health-topic

Appendix B – Sample Menus

Sample Menu 1

Breakfast (376 kcal, 70 g carbs, 6 g fat, 16 g protein, 421 mg sodium, 33 g sugar)
- ½ cup whole grain cereal with raisins, low-fat
- 1 cup 1% milk
- 1 slice 100% whole wheat toast
- 1 tbsp jelly/jam

Snack (285 kcal, 34 g carbs, 6 g fat, 26 g protein, 285 mg sodium, 9 g sugar)
- 1 cup plain nonfat Greek yogurt
- ¼ cup grain cereal/oats (on top of yogurt)

Lunch (558 kcal, 97 g carbs, 9 g fat, 26 g protein, 495 mg sodium, 22 g sugar)
- 3 oz Oven-roasted Chicken Breast
- 1 cup Brown Rice
- 1 cup Mixed Vegetables
- 1 medium fruit

Snack (427 kcal, 32 g carbs, 27 g fat, 13 g protein, 107 sodium, 24 g sugar)
- 1/2 cup trail mix (nuts, dried fruit, seeds, dark chocolate chips)

Dinner (487 kcal, 67 g carbs, 11 g fat, 33 g protein, 904 sodium, 12 g sugar)
- 3 oz Flank Steak
- 2/3 cup Rice Pilaf
- ½ cup baked sweet potato fries
- 1 cup steamed collard greens
- ½ cup grapes

Totals: 2133 kcal, 114 g protein, 300 g carbs (100 g sugar), 59 g fat, 2200 mg sodium

Sample Menu 2

Breakfast (518 kcal, 74 g carbs, 9 g fat, 41 g pro, 528 mg sodium, 25 g sugar)

- 1 eggs, scrambled
- 1 slice 100% whole wheat toast
- 1 cup plain nonfat Greek yogurt
- ¼ cup grain cereal/oats (on top of yogurt)
- 1 cup mixed berries

Snack (188 kcal, 14 g carbs, 14 g fat, 7 g protein, 0 mg sodium, 7 g sugar)

- 3 tbsp whole almonds
- ½ cup fresh fruit

Lunch (534 kcal, 88 g carbs, 5 g fat, 19 g protein, 548 mg sodium, 20 g sugar)

- 3 oz teriyaki (low sodium) salmon
- 1 cup stir-fried vegetables
- 1 cup Brown Rice
- 1 medium fruit

Snack (200 kcal, 20 g carbs, 10 g fat, 10 g protein, 370 mg sodium, 1 g sugar)

- 1 oz nonfat or light butter popcorn
- 1 part-skim cheese stick or 1 oz low fat cheese

Dinner (514 kcal, 51 g carbs, 21 g fat, 26 g protein, 531 mg sodium, 20 g sugar)

- 3 oz baked pork loin
- 2 oz square cornbread
- ½ cup natural low sodium applesauce
- 1 cup steamed baby carrots

Totals: 1,954 kcal, 247 g carbs, 59 g fat, 103 g protein, 1,977 mg sodium, 73 g sugar

Appendix C - Meal Planning Resources

Recipe Resources

1. https://healthyeating.nhlbi.nih.gov/default.aspx
2. https://healthyeating.nhlbi.nih.gov/pdfs/Dinners_Cookbook_508-compliant.pdf
3. https://www.mayoclinic.org/healthy-lifestyle/recipes/dash-diet-recipes/rcs-20077146
4. https://www.foodnetwork.com/healthyeats/recipes ‘
5. https://www.tasteofhome.com/collection/dash-diet-recipes/view-all/
6. http://thedashdiet.net/

Sample Recipes

1) **Cinnamon-glazed Baby Carrots**
   a) 4 cups baby carrots, rinsed and split lengthwise if very thick (or frozen pre-sliced carrots); 2 tbsp soft tub margarine; 2 tbsp brown sugar; ½ tsp ground cinnamon; 1/8 tsp salt
   b) Directions
      i) Place the carrots in a small saucepan. Add just enough water to barely cover the carrots. Cover. Bring to a boil. Reduce heat to medium. Cook for 7–8 minutes, just until the carrots are easily pierced with a sharp knife.
      ii) While the carrots are cooking, combine margarine, brown sugar, cinnamon, and salt in a small saucepan, and melt together over low heat (or put in a microwave-safe bowl and microwave for a few seconds on high power, until margarine is mostly melted). Stir well to combine ingredients.
      iii) Drain carrots, leaving them in the saucepan. Pour cinnamon mixture over carrots. Cook and stir over medium heat for 2–3 minutes, just until the carrots are thoroughly coated and the glaze thickens slightly. Serve warm.
2) **Good-for-you Cornbread**
   a) 1 cup cornmeal; 1 cup flour; ¼ cup sugar; 1 tsp baking powder; 1 cup low-fat (1%) buttermilk; 1 large egg; ¼ cup soft tub margarine; 1 tsp vegetable oil (to grease baking pan)
   b) Directions
      i) Preheat oven to 350 °F.
      ii) Mix together cornmeal, our, sugar, and baking powder.
      iii) In another bowl, combine buttermilk and egg. Beat lightly. Slowly add buttermilk and egg mixture to dry ingredients. Add margarine and mix for 1 minute.
      iv) Bake for 20–25 minutes in an 8- by 8-inch, greased baking dish. Cool. Cut into 10 squares.

3) **Greek Style Flank Steak with tangy yogurt sauce**
    a) 1 beef flank steak (12 oz)
    b) For marinade: ¼ cup lemon juice; 1 tbsp olive oil; 2 tsp fresh oregano, rinsed dried and chopped (or ½ tsp dried); 1 tbsp garlic, minced (about 2-3 cloves)
    c) For yogurt sauce: 1 cup cucumber, peeled, seeded, and chopped; 1 cup nonfat plain yogurt; 2 tbsp lemon juice; 1 tbsp fresh dill rinsed dried and chopped (or ½ tsp dried); 1 tbsp garlic, minced (about 2-3 cloves); ½ tsp salt
    d) Directions
        i) For the marinade, combine lemon juice, olive oil, oregano, and garlic in a large bowl.
        ii) Lay steak in a container with sides and pour marinade over the steak. Let the steak marinate for at least 20 minutes or up to 24 hours, turning several times.
        iii) Combine all the ingredients for the yogurt sauce. Set yogurt sauce aside for at least 15 minutes to blend flavors. (Sauce can be prepared up to 1 hour in advance and refrigerated.)
        iv) Preheat oven broiler on high temperature, with the rack 3 inches from heat source.
        v) Broil steak for about 10 minutes on each side (to a minimum internal temperature of 145 F). Let cool for 5 minutes before carving.
        vi) Slice thinly across the grain into 12 slices (1 ounce each).*
        vii) Serve three slices of the steak with 1⁄2 cup yogurt sauce on the side.
4) **Grilled Tuna with Chickpea and Spinach salad**
    a) 1 Tbsp olive or canola oil; 1 Tbsp garlic, minced (about 2–3 cloves); 2 Tbsp lemon juice; 1 Tbsp oregano, minced (or 1 tsp dried); 12 oz tuna steaks, cut into 4 portions (3 oz each)
    b) For salad: ½ can (15½ oz) low-sodium chickpeas (or garbanzo beans), drained and rinsed; ½ bag (10 oz) leaf spinach, rinsed and dried; 1 Tbsp lemon juice; 1 medium tomato, rinsed and cut into wedges; 1/8 tsp salt; 1/8 tsp ground black pepper
    c) Directions
        i) Preheat grill pan or oven broiler (with the rack 3 inches from heat source) on high temperature.
        ii) Combine oil, garlic, lemon juice, and oregano, and brush over tuna steaks. Marinate for 5–10 minutes.
        iii) Meanwhile, combine all salad ingredients. (Salad can be made up to 2 hours in advance and refrigerated.)
        iv) Grill or broil tuna on high heat for 3–4 minutes on each side until the flesh is opaque and separates easily with a fork (to a minimum internal temperature of 145 °F).
        v) Serve one tuna steak over 1 cup of mixed salad.
5) **Mixed Veggies # 1**
    a) Asparagus; bell peppers; mushrooms
    b) Roasted or sautéed with olive or vegetable oil
6) **Mixed Veggies # 2**
    a) Zucchini/squash; carrots; green beans
    b) Steamed
7) **Oven-crusted Chicken Breast**

a) For Chicken: 4 boneless, skinless chicken breasts (3 oz each); 1 egg white; 1 cup fat-free evaporated milk; 1 cup breadcrumbs; ¼ cup rolled oats, crushed (pulse a few times in the food processor or crush between fingers to make smaller pieces); 1 cup whole-wheat flour; 2 tbsp olive oil or vegetable oil
b) For Salad: 2 tbsp lemon juice; ½ tbsp. olive oil; 4 cups red leaf lettuce, rinsed and dried; 1 cup cherry tomatoes, rinsed and halved; ¼ tsp salt; ¼ tsp ground black pepper
c) Directions
    i) Preheat oven to 350 °F.
    ii) Place chicken in a freezer bag with the air squeezed out, and pound each breast down to 1⁄2-inch thickness.
    iii) Combine the egg white and evaporated milk in a bowl and mix well. In a separate bowl, combine the breadcrumbs and crushed oats, and mix well.
    iv) Coat the chicken breasts in flour and shake off the excess. Dip the chicken breasts in the egg and milk mixture and drain off the excess. Then dip the chicken breasts in the breadcrumb mixture to coat and shake off the excess. After all chicken breasts have been coated, discard any leftover breading mixture.
    v) Heat oil in a large sauté pan. Stir fry the chicken over medium-high heat on one side until golden brown, about 2–3 minutes. Turn carefully, and pan fry the second side for an additional 2–3 minutes or until golden brown. Remove from the pan, and place on paper towels to soak up excess oil. Place on baking sheet, and finish cooking in a 350°F oven for about 5–8 minutes (to a minimum internal temperature of 165°F).
    vi) For the salad, combine lemon juice and olive oil, and mix well to make a dressing. Toss the lettuce leaves and cherry tomatoes with the dressing, salt, and pepper.
    vii) Serve 1 cup salad with one piece of chicken.

8) Parmesan Rice and Pasta Pilaf

a) 2 tbsp olive oil; ½ cup thin spaghetti, finely broken, uncooked; 2 tbsp onion, diced; 1 cup long-grain white rice, uncooked; 1¼ cups chicken broth, hot; 1¼ cups water, hot; ¼ tsp ground white pepper; 1 bay leaf; 2 tbsp shredded parmesan cheese
b) Directions
    i) In a large sauté pan, heat the oil. Sauté vermicelli and onion until golden brown (for about 2–4 minutes) over medium-high heat. Drain off oil.
    ii) Add rice, chicken broth, water, pepper, and bay leaf. Cover and simmer for 15–20 minutes. Fluff with fork. Cover and let stand for 5 minutes. Remove bay leaf.
    iii) Sprinkle with shredded parmesan cheese and serve immediately.

9) Pork Mignons with French Applesauce

a) 1 pair pork tenderloins (about 2 lbs.); 1⁄4 tsp salt; 1/8 tsp ground black pepper; 2 medium apples, rinsed and cored, but not peeled (try Golden Delicious or Rome); 2 tbsp dark seedless raisins; 2 tbsp walnut, broken into coarse pieces; ½ tsp cinnamon; Cooking spray
b) Directions
    i) Preheat oven broiler on high temperature, with the rack 3 inches from heat source.
    ii) Cover broiler pan with aluminum foil for easy cleanup. Spray foil lightly with cooking spray. Set aside.

iii) Cut 8 slices (pork rounds), each 1 1⁄2 inches thick, from the center of the pair of pork tenderloins. Refrigerate or freeze the ends for another use. Place pork rounds on the foil-covered broiler pan. Sprinkle with salt and pepper. Set aside a few minutes while broiler heats.

iv) Meanwhile, heat 1⁄2 cup water to boiling in a medium nonstick pan. Slice cored apples from top to bottom in 1⁄4-inch wide pieces. Add apples, raisins, walnuts, and cinnamon to boiling water. Reduce heat to medium. Cover. Simmer, stirring occasionally, until apples are soft and easily pierced with a fork. Set aside until pork is cooked.

v) Broil pork for 5–10 minutes per side (to a minimum internal temperature of 160 °F).

vi) To serve, place two pork rounds on each dinner plate. Top with ¼ of the applesauce.

10) Savory Brown Rice

a) 1 tbsp olive oil; 1 cup onion, chopped; 1 cup portabella mushrooms, rinsed, halved, thinly sliced; ½ cup celery, rinsed and finely diced; 2 cups low-sodium chicken broth; 1 cup instant brown rice, uncooked; ¼ cup dried parsley; ¼ tsp salt; Add black pepper to taste

b) Directions

i) In a 4-quart saucepan, warm olive oil over medium heat. Add onion, mushrooms, and celery. Cook and stir for 5–7 minutes, until all vegetables are soft, but not brown.

ii) Stir in the chicken broth, brown rice, parsley, salt, and pepper. Cover. Bring to a boil over high heat.

iii) Reduce heat to medium. Cook according to brown rice package directions, about 5–10 minutes. Drain off any excess liquid. Fluff with a fork. Serve immediately.

11) Teriyaki-glazed salmon with stir-fried vegetables

a) For Salmon: 2 tbsp light teriyaki sauce; ¼ cup mirin (or sweet rice wine); 2 tbsp rice vinegar; 2 tbsp scallions (green onions), rinsed and minced; 1½ tbsp. ginger, minced (or 1 tsp ground); 12 oz salmon fillets, cut into 4 portions (3 oz each)

b) For Vegetables: 1 bag (12 oz) frozen vegetable stir-fry; ½ tbsp peanut oil or vegetable oil; ½ tbsp. garlic, minced (about 1 clove); 1 tbsp ginger, minced (or 1 tsp ground); 1 tbsp scallions (green onions), rinsed and minced; 1 tbsp lite soy sauce

c) Directions

i) Thaw frozen vegetables in the microwave (or place entire bag in a bowl of hot water for about 10 minutes). Set aside until step 7.

ii) Preheat oven to 350 F.

iii) Combine teriyaki sauce, mirin, rice vinegar, scallions, and ginger. Mix well. Pour over salmon and marinate for 10–15 minutes.

iv) Remove salmon from the marinade and discard unused portion.

v) Place salmon on a baking sheet and bake for 10–15 minutes or until fish flakes easily with a fork in the thickest part (to a minimum internal temperature of 145 °F).

vi) Meanwhile, heat oil in a large wok or sauté pan. Add garlic, ginger, and scallions, and cook gently but do not brown, about 30 seconds to 1 minute.

vii) Add vegetables, and continue to stir fry for 2–3 minutes or until heated through. Add soy sauce.

viii) Serve one piece of salmon with 1 cup of vegetables.

d) ***Tip:*** Try serving with steamed rice or Asian-style noodles (soba or udon).

Food Intake Record

Day 1 2 3 4 **Date: ______________**

Circle one option

Meal (breakfast, lunch, dinner, snack)	**Time**	**Meal Location (restaurant, home, work, etc.)**	**Name of Food Item or Beverage (provide as much detail as possible, *one food item per line)***	**Amount consumed (cups, tsp., Tbsp., ounces, etc.)**

References

1. Kessler RC, Bromet EJ. The Epidemiology of Depression Across Cultures. *Ann Rev Public Health*. 2013;34:119-138.

2. Weinberger AH, Gbedemah M, Martinez AM, Nash D, Galea S, Goodwin RD. Trends in depression prevalence in the USA from 2005 to 2015: widening disparities in vulnerable groups. *Psychol Med*. 2018;48:1308-1315.

3. González HM, Tarraf W, Whitfield KE, Vega WA. The epidemiology of major depression and ethnicity in the United States. *J Psychiatr Res*. 2010;44:1043-1051.

4. Read J, Sharpe L, Modini M, Dear BF. Multimorbidity and Depression: A Systematic Review and Meta-analysis. *J Affect Dis* 2017;221:36-46.

5. Vyas, Ami, B.Pharm., M.B.A, Sambamoorthi U, Ph.D. Multimorbidity and depression treatment. *Gen Hosp Psychiatry*. 2011;33:238-245.

6. Lopresti AL, Hood SD, Drummond PD. A review of lifestyle factors that contribute to important pathways associated with major depression: Diet, sleep and exercise. *J Affect Dis*. 2013;148:12-27.

7. Opie RS, O'Neil A, Itsiopoulos C, Jacka FN. The impact of whole-of-diet interventions on depression and anxiety: a systematic review of randomised controlled trials. *Public Health Nutr*. 2015;18:2074-2093.

8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 5th ed. Washington, D.C.: American Psychiatric Association; 2013.

9. Holthoff VA, Beuthien-Baumann B, Zündorf G, et al. Changes in brain metabolism associated with remission in unipolar major depression. *Acta Psychiatr Scand*. 2004;110:184-194.

10. Martinot JL, Hardy P, Feline A, et al. Left prefrontal glucose hypometabolism in the depressed state: a confirmation. *Am J Psychiatry*. 1990;147:1313-1317.

11. Dunn RT, Kimbrell TA, Ketter TA, et al. Principal components of the beck depression inventory and regional cerebral metabolism in unipolar and bipolar depression. *Biol Psychiatry*. 2002;51:387-399.

12. Kimbrell TA, Ketter TA, George MS, et al. Regional cerebral glucose utilization in patients with a range of severities of unipolar depression. *Biol Psychiatry*. 2002;51:237-252.

13. Kahl KG, M.D, Georgi K, Bleich S, et al. Altered DNA methylation of glucose transporter 1 and glucose transporter 4 in patients with major depressive disorder. *J Psychiatr Res*. 2016;76:66-73.

14. Mocking RJT, Verburg HF, Westerink AM, et al. Fatty acid metabolism and its longitudinal relationship with the hypothalamic–pituitary–adrenal axis in major depression: Associations with prospective antidepressant response. *Psychoneuroendocrinology*. 2015;59:1-13.

15. Shimizu E, Hashimoto K, Okamura N, et al. Alterations of serum levels of brain-derived neurotrophic factor (BDNF) in depressed patients with or without antidepressants. *Biol Psychiatry*. 2003;54:70-75.

16. Pan W, Banks WA, Fasold MB, Bluth J, Kastin AJ. Transport of brain-derived neurotrophic factor across the blood–brain barrier. *Neuropharmacology*. 1998;37:1553-1561.

17. Lee B, Kim H, Park S, Kim Y. Decreased plasma BDNF level in depressive patients. *J of Affect Dis*. 2006;101:239-244.

18. Sözeri-Varma G, Enli Y, Toker-Uğurlu T, Alaçam H, Kalkan-Oğuzhanoğlu N. Decreased serum BDNF levels in major depressive patients. *Neurol Psychiatr Brain Res*. 2011;17:84-88.

19. Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry J. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. *Psychiatr Res*. 2002;109:143-148.

20. Aydemir Ö, Deveci A, Taskin OE, Taneli F, Esen-Danaci A. Serum brain-derived neurotrophic factor level in dysthymia: A comparative study with major depressive disorder. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2007;31:1023-1026.

21. Huang T, Lee C, Liu Y. Serum brain-derived neurotrophic factor levels in patients with major depression: Effects of antidepressants. *J Psychiatr Res*. 2007;42:521-525.

22. Wolkowitz OM, Wolf J, Shelly W, et al. Serum BDNF levels before treatment predict SSRI response in depression. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 2011;35:1623-1630.

23. Birkenhäger TK, Geldermans S, Van den Broek, Walter W, van Beveren N, Fekkes D. Serum brain-derived neurotrophic factor level in relation to illness severity and episode duration in patients with major depression. *J Psychiatr Res*. 2011;46:285-289.

24. Gawryluk JW, Wang J, Andreazza AC, Shao L, Young LT. Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. *Int J Neuro-Psychopharmacol*. 2011;14:123-130.

25. Kodydková J, Vávrová L, Zeman M, et al. Antioxidative enzymes and increased oxidative stress in depressive women. *Clin Biochem*. 2009;42:1368-1374.

26. Gałecki P, Szemraj J, Bieńkiewicz M, Florkowski A, Gałecka E. Lipid peroxidation and antioxidant protection in patients during acute depressive episodes and in remission after fluoxetine treatment. *Pharmacoll Rep : PR*. 2009;61:436.

27. Lindqvist D, Dhabhar FS, James SJ, et al. Oxidative stress, inflammation and treatment response in major depression. *Psychoneuroendocrinology*. 2016;76:197-205.

28. Rybka J, Kędziora-Kornatowska K, Banaś-Leżańska P, et al. Interplay between the pro-oxidant and antioxidant systems and proinflammatory cytokine levels, in relation to iron metabolism and the erythron in depression. *Free Radic Biol Med*. 2013;63:187-194.

29. Bilici M, Efe H, Köroğlu MA, Uydu HA, Bekaroğlu M, Değer O. Antioxidative enzyme activities and lipid peroxidation in major depression: alterations by antidepressant treatments. *J Affect Dis*. 2001;64:43-51.

30. Sarandol A, Sarandol E, Eker SS, Erdinc S, Vatansever E, Kirli S. Major depressive disorder is accompanied with oxidative stress: short-term antidepressant treatment does not alter oxidative–antioxidative systems. *Hum Psychopharmacol: Clin Exp*. 2007;22:67-73.

31. Simon G, Von Korff M, Saunders K, et al. Association Between Obesity and Psychiatric Disorders in the US Adult Population. *Arch Gen Psychiatry*. 2006;63:824-830.

32. Roberts RE, Deleger S, Strawbridge WJ, Kaplan GA. Prospective association between obesity and depression: evidence from the Alameda County Study. *Int J Obes*. 2003;27:514-521.

33. Strine TW, M.P.H, Mokdad AH, Ph.D, Dube, Shanta R., Ph.D., M.P.H, et al. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatry*. 2008;30:127-137.

34. de Wit LM, van Straten A, van Herten M, Penninx, B. W. J. H, Cuijpers P. Depression and body mass index, a u-shaped association. *BMC Public Health*. 2009;9:14.

35. Carpenter K, Hasin D, Allison D, Faith M. Relationships Between Obesity and DSM-IV Major Depressive Disorder, Suicide Ideation, and Suicide Attempts: Results From a General Population Study. *Am J Public Health*. 2000;90:251-257.

36. Scott KM, Bruffaerts R, Simon GE, et al. Obesity and mental disorders in the general population: results from the world mental health surveys. *Int J Obes*. 2008;32:192-200.

37. Onyike CU, Crum RM, Lee HB, Lyketsos CG, Eaton WW. Is Obesity Associated with Major Depression? Results from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol*. 2003;158:1139-1147.

38. Dixon JB, Dixon ME, O'Brien PE. Depression in Association With Severe Obesity: Changes With Weight Loss. *JAMA Intern Med*. 2003;163:2058-2065.

39. Kloiber S, Ising M, Reppermund S, et al. Overweight and Obesity Affect Treatment Response in Major Depression. *Biol Psychiatry*. 2007;62:321-326.

40. Westman E, Feinman R, Mavropoulos J, et al. Low-carbohydrate nutrition and metabolism. *Am J Clin Nutr*. 2007;86:276-284.

41. Freeman J, Veggiotti P, Lanzi G, Tagliabue A, Perucca E. The Ketogenic diet: from molecular mechanisms to clinical effects. *Epilepsy Res*. 2006;68:145-180.

42. Hartman AL, Gasior M, Vining EP, Rogawski MA. The Neuropharmacology of the Ketogenic Diet. *Pediatr Neurol*. 2007;36:281-292.

43. Manninen AH. Metabolic effects of the very-low-carbohydrate diets: misunderstood "villains" of human metabolism. *J Int Soc Sports Nutr*. 2004;1:7-11.

44. Zhang Y, Kuang Y, Xu K, et al. Ketosis Proportionately Spares Glucose Utilization in Brain. *J Cereb Blood Flow Metab.* London, England: SAGE Publications; 2013;33:1307-1311.

45. Bough KJ, Wetherington J, Hassel B, et al. Mitochondrial biogenesis in the anticonvulsant mechanism of the ketogenic diet. *Ann Neurol*. 2006;60:223-235.

46. Genzer Y, Dadon M, Burg C, Chapnik N, Froy O. Effect of dietary fat and the circadian clock on the expression of brain-derived neurotrophic factor (BDNF). *Mol Cell Endocrinol*. 2016;430:49-55.

47. Marosi K, Kim SW, Moehl K, et al. 3-Hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. *J Neurochem*. 2016;139:769-781.

48. Vizuete AF, de Souza DF, Guerra MC, et al. Brain changes in BDNF and S100B induced by ketogenic diets in Wistar rats. *Life Sci*. 2013;92:923-928.

49. Yao J, Chen S, Mao Z, Cadenas E, Diaz Brinton R. 2-Deoxy-D-Glucose Treatment Induces Ketogenesis, Sustains Mitochondrial Function, and Reduces Pathology in Female Mouse Model of Alzheimer's Disease. *PLOS ONE*. 2011;6:e21788.

50. Milder JB, Liang L, Patel M. Acute oxidative stress and systemic Nrf2 activation by the ketogenic diet. *Neurobiol Dis*. 2010;40:238-244.

51. Noh HS, Hah Y, Nilufar R, et al. Acetoacetate protects neuronal cells from oxidative glutamate toxicity. *J Neurosci Res*. 2006;83:702-709.

52. Yang X, Cheng B. Neuroprotective and Anti-inflammatory Activities of Ketogenic Diet on MPTP-induced Neurotoxicity. *J Mol Neurosci*. 2010;42:145-153.

53. Jarrett S, Milder J, Liang L, Patel M. The ketogenic diet increases mitochondrial glutathione levels. *J Neurochem*. 2008;106:1044-1051.

54. Maalouf M, Sullivan PG, Davis L, Kim DY, Rho JM. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH oxidation. *Neurosci*. 2007;145:256-264.

55. Sullivan PG, Rippy NA, Dorenbos K, Concepcion RC, Agarwal AK, Rho JM. The ketogenic diet increases mitochondrial uncoupling protein levels and activity. *Ann Neurol*. 2004;55:576-580.

56. Greco T, Glenn TC, Hovda DA, Prins ML. Ketogenic diet decreases oxidative stress and improves mitochondrial respiratory complex activity. *J Cereb Blood Flow Metab*. 2016;36:1603-1613.

57. Ziegler D, Ribeiro L, Hagenn M, et al. Ketogenic Diet Increases Glutathione Peroxidase Activity in Rat Hippocampus. *Neurochem Res*. 2003;28:1793-1797.

58. Murphy P, Likhodii S, Nylen K, Burnham WM. The antidepressant properties of the ketogenic diet. *Biol Psychiatry*. 2004;56:981-983.

59. Huang C, Wang P, Xu X, et al. The ketone body metabolite β-hydroxybutyrate induces an antidepression-associated ramification of microglia via HDACs inhibition-triggered Akt-small RhoGTPase activation. *Glia*. 2018;66:256-278.

60. Chen L, Miao Z, Xu X. B-hydroxybutyrate alleviates depressive behaviors in mice possibly by increasing the histone3-lysine9-B-hydroxybutyrylation. *Biochem Biophys Res Commun*. 2017;490:117-122.

61. Sussman D, Germann J, Henkelman M. Gestational ketogenic diet programs brain structure and susceptibility to depression & anxiety in the adult mouse offspring. *Brain Behav*. 2015;5:e00300-n/a.

62. Rosen JC, Hunt DA, Sims EA, Bogardus C. Comparison of carbohydrate-containing and carbohydrate-restricted hypocaloric diets in the treatment of obesity: effects of appetite and mood. *Am J Clin Nutr*. 1982;36:463.

63. Wells A, Read N. Influences of Fat, Energy, and Time of Day on Mood and Performance. . 1994;59:1069-1076.

64. D'Anci KE, Watts KL, Kanarek RB, Taylor HA. Low-carbohydrate weight-loss diets. Effects on cognition and mood. *Appetite*. 2009;52:96-103.

65. Halyburton AK, Brinkworth GD, Wilson CJ, et al. Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. *Am J Clin Nutr*. 2007;86:580.

66. Yancy W, Olsen M, Guyton J, Bakst R, Westman E. A Low Carbohydrate, Ketogenic Diet versus a Low Fat Diet To Treat Obesity and Hyperlipidemia. *Ann Intern Med.* American College of Physicians; 2004.

67. Samaha FF, Iqbal N, Seshadri P, et al. A Low-Carbohydrate as Compared with a Low-Fat Diet in Severe Obesity. *N Engl J Med*. 2003;348:2074-2081.

68. Foster GD, Wyatt HR, Hill JO, et al. A Randomized Trial of a Low-Carbohydrate Diet for Obesity. *N Engl J Med*. 2003;348:2082-2090.

69. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. A Randomized Trial Comparing a Very Low Carbohydrate Diet and a Calorie-Restricted Low Fat Diet on Body Weight and Cardiovascular Risk Factors in Healthy Women. *J Clin Endocrinol Metab*. 2003;88:1617-1623.

70. Volek J, Sharman M, Gómez A, et al. Comparison of energy-restricted very low-carbohydrate and low-fat diets on weight loss and body composition in overweight men and women. *Nutr Metab*. 2004;1:13.

71. Vetter M, Iqbal N, Volger S. Long-Term Effects of Low-Carbohydrate Versus Low-Fat Diets in Obese Persons. *Ann Intern Med.* American College of Physicians; 2010.

72. Shai I, Schwarzfuchs D, Henkin Y, et al. Weight Loss with a Low-Carbohydrate, Mediterranean, or Low-Fat Diet. *N Engl J Med*. 2008;359:229-241.

73. Dyson PA, Beatty S, Matthews DR. A low-carbohydrate diet is more effective in reducing body weight than healthy eating in both diabetic and non-diabetic subjects. *Diabet Med*. 2007;24:1430-1435.

74. Bazzano LA, Hu T, Reynolds K, et al. Effects of low-carbohydrate and low-fat diets: a randomized trial. *Ann Intern Med*. 2014;161:309-318.

75. Castaldo G, Monaco L, Castaldo L, Galdo G, Cereda E. An observational study of sequential protein-sparing, very low-calorie ketogenic diet (Oloproteic diet) and hypocaloric Mediterranean-like diet for the treatment of obesity. *Int J Food Sci Nutr*. 2016;67:696-706.

76. Dyson PA, Beatty S, Matthews DR. An assessment of low-carbohydrate or low-fat diets for weight loss at 2 year's follow-up. *Diabet Med*. 2010;27:363-364.

77. LaRosa J, Fry A, Muesing R, Rosing D. Effects of high protein, low carbohydrate dieting on plasma lipoproteins and body weight. *J Am Diet Assoc.* Elsevier; 1980.

78. Volek JS, Sharman MJ, Love DM, et al. Body composition and hormonal responses to a carbohydrate-restricted diet. *Metabolism*. 2002;51:864-870.

79. Urbain P, Strom L, Morawski L, Wehrle A, Deibert P, Bertz H. Impact of a 6-week non-energy-restricted ketogenic diet on physical fitness, body composition and biochemical parameters in healthy adults. *Nutr Metab*. 2017;14.

80. Westman EC, Yancy WS, Edman JS, Tomlin KF, Perkins CE. Effect of 6-month adherence to a very low carbohydrate diet program. *Am J Med*. 2002;113:30-36.

81. Soenen S, Bonomi AG, Lemmens SGT, et al. Relatively high-protein or 'low-carb' energy-restricted diets for body weight loss and body weight maintenance? *Physiol Behav*. 2012;107:374-380.

82. Iqbal N, Vetter ML, Moore RH, et al. Effects of a Low-intensity Intervention That Prescribed a Low-carbohydrate vs. a Low-fat Diet in Obese, Diabetic Participants. *Obesity*. 2010;18:1733-1738.

83. Lim SS, Noakes M, Keogh JB, Clifton PM. Long-term effects of a low carbohydrate, low fat or high unsaturated fat diet compared to a no-intervention control. *Nutr Metab Cardiovasc Dis*. 2009;20:599-607.

84. Gardner CD, Trepanowski J, King A, et al. Neither insulin secretion nor genotype pattern modify 12-month weight loss effects of healthy low-fat vs. healthy low-carbohydrate diets among adults with obesity. *Circulation*. 2017;135.

85. Brinkworth GD, Noakes M, Buckley JD, Keogh JB, Clifton PM. Long-term effects of a very-low-carbohydrate weight loss diet compared with an isocaloric low-fat diet after 12 mo. *Am J Clin Nutr*. 2009;90:23-32.

86. Leite JO, DeOgburn R, Ratliff JC, et al. Low-carbohydrate diet disrupts the association between insulin resistance and weight gain. *Metabolism*. 2009;58:1116-1122.

87. Tay J, Brinkworth GD, Noakes M, Keogh J, Clifton PM. Metabolic Effects of Weight Loss on a Very-Low-Carbohydrate Diet Compared With an Isocaloric High-Carbohydrate Diet in Abdominally Obese Subjects. *J Am Coll Cardiol*. 2008;51:59-67.

88. Meckling KA, O'Sullivan C, Saari D. Comparison of a Low-Fat Diet to a Low-Carbohydrate Diet on Weight Loss, Body Composition, and Risk Factors for Diabetes and Cardiovascular Disease in Free-Living, Overweight Men and Women. *J Clin Endocrinol Metab*. 2004;89:2717-2723.

89. Stern L, Iqbal N, Seshadri P, Chicano K. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: One-year follow-up of a randomized trial. *ACC Curr J Rev*. 2004;13:18.

90. Noakes M, Foster PR, Keogh JB, James AP, Mamo JC, Clifton PM. Comparison of isocaloric very low carbohydrate/high saturated fat and high carbohydrate/low saturated fat diets on body composition and cardiovascular risk. *Nutr Metab*. 2006;3:7.

91. Johnston CS, Tjonn SL, Swan PD, White A, Hutchins H, Sears B. Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets. *Am J Clin Nutr*. 2006;83:1055-1061.

92. Gardner CD, Offringa LC, Hartle JC, Kapphahn K, Cherin R. Weight loss on low-fat vs. low-carbohydrate diets by insulin resistance status among overweight adults and adults with obesity: A randomized pilot trial. *Obesity*. 2016;24:79-86.

93. Foster GD, Wyatt HR, Hill JO, et al. Weight and metabolic outcomes after 2 years on a low-carbohydrate versus low-fat diet: a randomized trial. *Ann Intern Med*. 2010;153:147-157.

94. Dashti HM, Bo-Abbas YY, Asfar SK, et al. Ketogenic diet modifies the risk factors of heart disease in obese patients. *Nutrition*. 2003;19:901-902.

95. Wood RJ, Volek JS, Liu Y, Shachter NS, Contois JH, Fernandez ML. Carbohydrate restriction alters lipoprotein metabolism by modifying VLDL, LDL, and HDL subfraction distribution and size in overweight men. *J Nutr*. 2006;136:384.

96. Volek J, Phinney S, Forsythe C, et al. Carbohydrate Restriction has a More Favorable Impact on the Metabolic Syndrome than a Low Fat Diet. *Lipids*. 2009;44:297-309.

97. Forsythe C, Phinney S, Fernandez M, et al. Comparison of Low Fat and Low Carbohydrate Diets on Circulating Fatty Acid Composition and Markers of Inflammation. *Lipids*. 2008;43:65-77.

98. Dashti HM, Mathew TC, Hussein T, et al. Long-term effects of a ketogenic diet in obese patients. *Exp Clin Cardiol*. 2004;9:200.

99. Cardillo S, Seshadri P, Iqbal N. The effects of a low-carbohydrate versus low-fat diet on adipocytokines in severely obese adults: three-year follow-up of a randomized trial. *Eur Rev Med Pharmacol Sci* 2006;10:99.

100. Sharman MJ, Volek JS. Weight loss leads to reductions in inflammatory biomarkers after a very-low-carbohydrate diet and a low-fat diet in overweight men. *Clin Sci*. 2004;107:365-369.

101. American College of Sports Medicine. *ACSM's Guidelines for Exercise Testing and Prescription.* 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2017.

102. Beck A, Steer R, Brown G. Manual for the beck depression inventory-II. 1996.

103. Beck AT, Epstein N, Brown G, Steer RA. An Inventory for Measuring Clinical Anxiety. *J Consult Clin Psychol*. 1988;56:893-897.

104. Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35:1381-1395.

105. Breland J, Phibbs C, Hoggatt K, et al. The Obesity Epidemic in the Veterans Health Administration: Prevalence Among Key Populations of Women and Men Veterans. *J Gen Intern Med*. 2017;32:11-17.