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AN EXAMINATION OF CHANGES IN DIET QUALITY, MEASURES OF INFLAMMATION, DEPRESSIVE SYMPTOMS, AND METABOLIC SYNDROME SEVERITY ACROSS THE FIRST SEMESTER IN COLLEGE

A Dissertation in

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Abstract

Metabolic Syndrome (MetS), a cluster of cardiometabolic abnormalities including elevated waist circumference, low high-density lipoprotein (HDL) cholesterol, high triglycerides, high blood pressure, and elevated fasting glucose, affects nearly 35% of American adults. The presence of MetS both predicts and contributes to the development of cardiovascular diseases and type 2 diabetes (i.e., cardiometabolic disease). MetS and cardiometabolic diseases are commonly comorbid with Major Depressive Disorder (MDD), the leading cause of disability in the United States. Chronic inflammation may drive the development of both MetS and MDD. While many factors influence inflammation, low diet quality may be particularly important due to the role of diet in regulating immune function. Poor diet quality is a leading modifiable contributor to MetS development, and is also associated with MDD. Primary prevention programs targeting diet quality could therefore be an effective means of reducing both MetS and MDD, possibly via reducing inflammation.

While the development of such primary prevention programs would be a valuable public health tool, efforts are limited by the lack of measures available to detect at-risk individuals prior to disease onset. Given that inflammation is a plausible mechanism driving MetS and MDD development, inflammatory markers may be a useful avenue for assessing long-term disease risk. However, circulating markers of inflammation are often below the level of measurable detection in young and healthy individuals, limiting their use in primary prevention research. *Ex vivo* lipopolysaccharide (LPS) stimulated cytokine production is less prone to floor effects, and may be a more viable marker of immune function in young samples. The present study examines concurrent associations among diet quality, depressive symptoms, MetS symptom severity, circulating cytokines, and *ex vivo* stimulated cytokine production in incoming college students, as well as change in these variables across the first semester.

A sample of 110 incoming first-year students was recruited at the Pennsylvania State University, University Park campus. Data were collected at two study visits. Visit 1 occurred

within the first 4 weeks of the fall 2021 semester; visit 2 occurred at the end of the same semester, during the last 2 weeks of classes. At each visit, participants' height, weight, waist circumference, blood pressure, HDL-cholesterol, triglycerides, fasting glucose, circulating cytokines, and *ex vivo* LPS stimulated cytokine production were assessed. Demographic information, diet quality, and depressive symptoms were also assessed at each visit.

Diet quality and MetS symptom severity were significantly correlated at both visit 1 (r = -.419, p = .001) and visit 2 (r = -.355, p = .001). After controlling for sleep quality, physical activity, and perceived stress in a regression model, diet quality still significantly predicted MetS symptom severity at both visit 1 (B = -0.024, p < .001) and visit 2 (B = -0.021, p < .001). In both the correlational and regression analyses, higher diet quality was associated with significantly lower (i.e., better) MetS symptom severity. Across the semester, diet quality significantly declined (mean change = -3.093, p = .008) while MetS symptom severity significantly increased (mean change = 0.152, p < .001).

In sum, these findings underscore the need for developing lifestyle-based primary prevention programs aimed at reducing cardiometabolic disease risk in younger individuals. The entry into college may be an ideal time to initiate such programs, particularly dietary interventions, to help attenuate the decline in diet quality and increase in MetS symptom severity that occurs across the first semester.

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Body Mass Index (BMI)

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Monounsaturated Fatty Acid (MUFA)

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National Health and Nutrition Examination Survey III (NHANES-III)

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Nucleotide-binding Oligomerization Domain (NOD)

Nucleotide-binding Oligomerization Domain-like receptor pyrin domain–containing-3 (NLRP3)

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Prevention with Mediterranean Diet (PREDIMED)

Research Electronic Data Capture (REDCap

Saturated Fatty Acid (SFA)

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Very Low-Density Lipoprotein Cholesterol (vLDL-C)

Chapter 1: Introduction

Metabolic Syndrome (MetS), a cluster of cardiovascular and metabolic (i.e., cardiometabolic) abnormalities including abdominal adiposity, dyslipidemia, hypertension, and insulin resistance (Alberti et al., 2009), is considered a precursor to cardiovascular disease (CVD) and metabolic diseases such as type 2 diabetes (T2D) (Wilson et al., 2005). More specifically, according to the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III (ATP-III) diagnostic criteria (see Table 1), MetS symptoms include a waist circumference of ≥ 40" for males or ≥ 35" for females, as well as low high-density lipoprotein cholesterol (HDL-C; males: < 40 mg/dL, females: < 50 mg/dL), high triglycerides (≥ 150 mg/dL), hypertension (blood pressure ≥ 130/85 mmHg), and elevated fasting glucose (≥ 100 mg/dL; NCEP Expert Panel, 2002). To meet full MetS criteria, an individual must present with at least 3 of these symptoms (NCEP Expert Panel, 2002). As of 2018, the most recent available data, 38.3% of American adults (age ≥ 20 years) met diagnostic criteria for MetS, and evidence suggests that rates of MetS have been increasing across time (Liang et al., 2021). Individuals with MetS have a 2-fold increase in odds of CVD morbidity and mortality compared to healthy individuals (Mottillo et al., 2010), and are 47% (females) to 62% (males) more likely to develop T2D within an 8-year period (Wilson et al., 2005). While more research is needed to fully delineate disease processes, known physiological drivers of MetS include abdominal obesity, insulin resistance, and chronic inflammation (Elks & Francis, 2010; Mechanick et al., 2020). Behavioral factors also play a key role in MetS development. For example, poor diet quality has consistently been linked to MetS symptoms (Kim, 2019; Tian et al., 2018; Yosaee et al., 2017), and is considered a leading modifiable risk factor for CVD (Kris-Etherton et al., 2020) and T2D (Ley et al., 2016). Diet therefore represents an excellent avenue for prevention and intervention efforts aimed at reducing MetS and associated cardiometabolic disease risk (Riccardi & Rivellese, 2000).

By college age, MetS symptoms are common, with 42-60% of students meeting at least one out of the five diagnostic criteria (Dalleck & Kjelland, 2012; Higgins et al., 2020). However, less than 7% of college students meet full MetS criteria (Dalleck & Kjelland, 2012; Higgins et al., 2020). Given that MetS is a chronic condition that increases in prevalence across the lifespan (Aguilar et al., 2015), primary prevention programs targeting younger populations prior to MetS development are warranted. Early identification of at-risk individuals in combination with lifestyle-based primary prevention programs could contribute to substantial reductions in long-term disease risk. The first semester of college may be a critically important period for the development of biobehavioral risk factors for MetS, as most incoming students experience significant lifestyle changes as part of the transition into independence (e.g., Jung et al., 2008; Wengreen & Moncur, 2009). For example, incoming first-year students typically experience declining diet quality (e.g., Butler et al., 2004), accompanied by increasing weight and/or body fat percentage (Keown et al., 2009; Mihalopoulos et al., 2008; Racette et al., 2005). Elevated BMI and body fat percentage promote the development of chronic inflammation (Calder et al., 2011; Nishimura et al., 2009); as such, increasing weight and body fat confer additional risk of MetS and associated diseases (Suzuki & Akamatsu, 2014). Incoming college students gain weight a rate that is significantly higher than that in the general population (Vadeboncoeur et al., 2015). On average, students gain 1.5kg in the first semester of college, with 23% of students gaining ≥ 5% of their baseline body weight (Wengreen & Moncur, 2009),

While first year weight gain is related to several lifestyle factors, diet quality is a major contributor: unhealthy diet, alcohol consumption, and frequency of snacking explain 23% of the variance in change in body mass index (BMI) across the first academic year (Pliner & Saunders, 2008). Of particular importance to the proposed study, most first-year students at the Pennsylvania State University, University Park (Penn State) campus are required to reside in on-campus housing. On-campus and off-campus residing students have comparable BMIs; however on-campus students tend to engage in significantly more physical activity compared to

off-campus students, while also consuming a lower quality diet (Yoon et al., 2014). Thus, while some research suggests that reduced physical activity is the primary driver of first-year weight gain (Jung et al., 2008), this does not appear to be the case for students who reside in on-campus housing, such as most first-year students at Penn State. Instead, weight gain in these students may be more closely related to decreasing diet quality.

A growing body of research suggests that dietary and nutritional factors are involved in the regulation of key inflammatory processes (Galland, 2010; Nobs et al., 2020). Poor diet quality has consistently been associated with chronic inflammation (Donath et al., 2019; Kiecolt-Glaser et al., 2015; Nobs et al., 2020), a primary driver of MetS, as well as cardiovascular and metabolic disease development (Das, 2010). For example, the Western dietary pattern is high in saturated fats, added sugars, and processed foods, and low in fiber; adherence to this dietary pattern is associated with the presence of chronic, low-grade inflammation (Christ et al., 2018; Nobs et al., 2020), and consequently with the development of MetS (Das, 2010; Drake et al., 2018), and downstream CVD and/or T2D (Stanhope et al., 2018). Individuals in the highest quintile for adherence to a Western dietary pattern (i.e., who have a low-quality diet) have an 18% increase in risk of MetS development across 9-years compared to the lowest quintile (Lutsey et al., 2008). Conversely, diets high in fruits and vegetables have been associated with reduced inflammation (Hosseini et al., 2018), and with reduced MetS risk (Kim, 2019; Tian et al., 2018). College students tend to consume a poor-quality diet that is in line with the Western dietary pattern (Pliner & Saunders, 2008) and is particularly low in fruits and vegetables (Kim, 2019; Pliner & Saunders, 2008; Tian et al., 2018); the diet quality of college students also tends to decline across time (Butler et al., 2004; Pliner & Saunders, 2008). Evidence suggests that inflammation can be attenuated via dietary improvements (Giugliano et al., 2006; O'Keefe et al., 2008), even in individuals with obesity (Tateya et al., 2013). Thus, research aimed at improving diet quality early in college may substantially reduce MetS, and thus long-term disease risk, in this vulnerable population.

In addition to diet, depression may also be an important risk factor for MetS development (East et al., 2010; Moradi et al., 2021). Major Depressive Disorder (MDD) is the most prevalent mental health disorder among first-year college students, with 48% reporting clinically significant depressive symptoms (Brandy et al., 2015). While some conflicting results have been found, largely due to methodological inconsistencies (Quirk et al., 2013), a growing body of evidence links poor diet quality to MDD and depressive symptoms. For example, a meta-analysis of 24 independent prospective cohort studies found that adherence to a healthy dietary pattern is associated with a 64-78% decrease in risk of developing MDD (Molendijk et al., 2018). The same meta-analysis reported that a high dietary inflammatory index score (i.e., a low-quality diet that is high in foods that promote inflammation and low in foods that attenuate inflammation) is associated with an 81% increase in MDD risk (Molendijk et al., 2018), highlighting the role of inflammation in the relationship between diet quality and depression. Thus, poor dietary habits may contribute to the high rate of depression in college students; ongoing depression, in turn, may further reduce students' diet quality across time (Jacka et al., 2015).

The relationship between MetS and MDD also appears to be bidirectional: across both sexes, a history of MDD is associated with a 34% increase in odds of developing MetS, while the presence of MetS is associated with a 27% increase in odds of developing MDD (Pan et al., 2012). Indeed, a history of MDD has been associated with up to a 60% increase in the odds of developing MetS in women, even after adjusting for demographic and lifestyle factors (Vaccarino et al., 2008). Further, a negative correlation has been found between levels of circulating pro-inflammatory markers and mental health in adults with MetS, suggesting that pro-inflammatory processes may partially explain the comorbidity between MDD and MetS (Kim et al., 2018). In addition to the notable effect of diet on MetS and its components (Fanelli et al., 2020), poor diet quality is also associated with increased risk of MDD and depressive symptoms (Berk & Jacka, 2019; Jacka et al., 2014; Molendijk et al., 2018), possibly due to the influence of dietary patterns and specific nutrients on inflammation (Galland, 2010; Molendijk et al., 2018;

Nobs et al., 2020). Rates of MDD have been increasing across time, particularly in the college student population (Xiao et al., 2017), and may be contributing to increasing rates of CVD (Hidaka, 2012). Additional research involving healthy samples (i.e., free of chronic disease) is needed in order to improve primary prevention strategies to reduce both the prevalence of MDD and long-term cardiometabolic disease risk.

Progress in primary prevention research to date has been hampered by the limited predictive capacity of current risk assessment tools. The Framingham Risk Score, for example, is the most widely used and well-validated measure of atherosclerotic CVD risk (Hemann et al., 2007); however, its predictive value is limited to 10-year risk (Alagona & Ahmad, 2015). Considering that CVD and metabolic diseases often begin to develop in childhood and continue to progress across the span of decades (Berenson, 2009; Hong, 2010; Muhlhausler & Smith, 2009; Williams et al., 1977), measures offering predictive value across longer timescales are needed to enable the development of effective primary prevention strategies. In addition, current risk assessment systems for atherosclerotic CVD fail to identify more than 50% of individuals who will go on to develop the disease (Alagona & Ahmad, 2015). This lack of predictive capacity is due, in part, to the fact that currently used biomarkers of disease risk are often difficult to measure in young, healthy (i.e., free of chronic disease) samples (Gilstrap & Wang, 2012).

Circulating pro-inflammatory cytokines, for example, are a commonly used biomarker of immune function, disease progression, and long-term disease risk (Kany et al., 2019). However, in young and/or healthy (i.e., free of chronic disease) individuals, levels of circulating pro-inflammatory cytokines often fall below the limits of measurable detection (Kleiner et al., 2013; Zhou et al., 2010); as a result, these individuals are assigned the same value, limiting the ability to draw meaningful conclusions. Further, evidence suggests that circulating inflammatory markers may not be an ideal marker of long-term disease risk even in young but unhealthy samples. For example, in adults, both obesity (Park et al., 2005) and MetS (Mohammadi et al., 2017) are independently associated with elevated levels of circulating pro-inflammatory

cytokines. In addition, circulating pro-inflammatory cytokines, including interleukin (IL)-6, IL-1β, and Tumor Necrosis Factor (TNF)-α, are higher in adolescents with obesity than those of a healthy weight (Al-Shorman et al., 2017). However, when comparing adolescents with obesity, pro-inflammatory cytokine levels do not significantly differ between those with and without MetS (Al-Shorman et al., 2017). Thus, while adolescents with MetS are theoretically in poorer health and at increased risk of developing cardiovascular and metabolic diseases, they are not distinguishable from metabolically healthy adolescents using common measures of inflammation.

Given the important role of inflammation and immune function in cardiometabolic disease pathology, development of a relevant measure that can be used in young samples and has prognostic value is imperative. While human subjects research on the topic is in its infancy, *ex vivo* stimulated inflammatory cytokine production has been posited as a candidate measure. For example, individuals with high blood pressure, a component of MetS, exhibit heightened pro-inflammatory cytokine production in response to *ex vivo* stimulation (Peeters et al., 2001). In addition, existing research using physically healthy samples has shown promising results. Past work by our lab group has found that *ex vivo* lipopolysaccharide (LPS) stimulated cytokine production is associated with the cortisol response to an acute laboratory stressor in healthy adults, suggesting that immune and endocrine stress reactivity levels are comparable (Davis et al., 2020). In addition, we found that measures of *ex vivo* LPS-stimulated cytokine production were highly correlated across two weeks within persons, making this a suitable measure for repeated measures research (Davis et al., 2020). Past research has also found that *ex vivo* stimulated inflammatory cytokine production is associated with depressive symptom severity: males generally show higher level of stimulated cytokine production with increasing depressive symptoms, while females have lower levels of cytokine production with increasing depressive symptoms (Knight et al., 2020; Majd et al., 2018). The same studies found no association between circulating cytokines and depressive symptoms (Knight et al., 2020; Majd et al., 2018).

This pattern of results suggests that *ex vivo* stimulated cytokine production may be a more appropriate tool for assessing immune function, and therefore long-term disease risk, in healthy individuals than circulating inflammatory markers. However, additional research is needed to determine the strength and nature of the relationship between *ex vivo* stimulated cytokine production and measures of physical and mental health.

The proposed study would seek to address this notable gap in the literature by examining the associations among diet quality, circulating pro-inflammatory cytokines, *ex vivo* LPS-stimulated inflammatory cytokine production, depressive symptoms, and MetS symptom severity during students' first semester in college; please see Figure 1 for a conceptual model. With the goals of aiding the development of indicators of cardiometabolic disease risk suitable for use in young samples and informing lifestyle-based primary prevention efforts, the proposed study would examine cross-sectional associations among potential risk factors and measures of current health status, as well as within-person changes in risk factors and health status across the first semester in college. The aims of the proposed study are thus fivefold:

Aim 1: Examine whether diet quality is associated with concurrent depressive symptoms and MetS symptom severity in first-semester college students at both study visits.

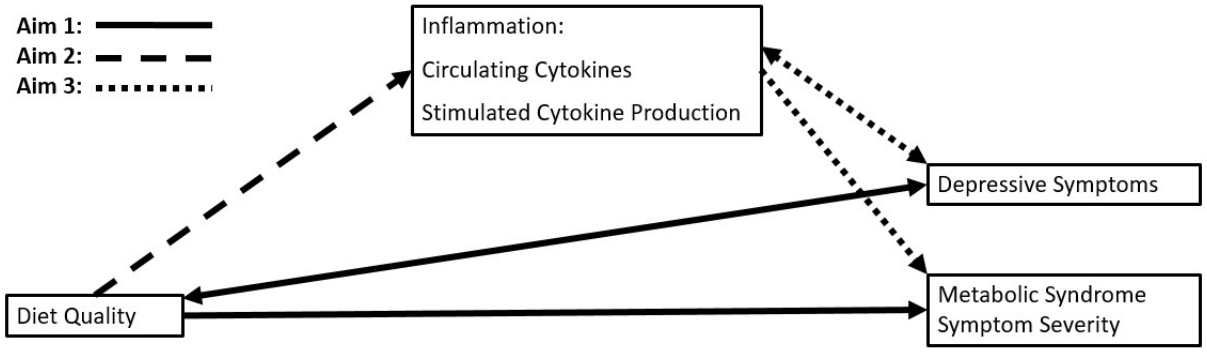
Aim 2: Test the association between diet quality and concurrent measures of circulating and stimulated pro-inflammatory cytokines at both study visits.

Aim 3: Examine whether heightened measures of inflammation are associated with greater concurrent depressive symptoms and MetS symptom severity at both study visits.

Aim 4: Explore whether diet quality, measures of inflammation, depressive symptoms, and MetS symptom severity change significantly from visit 1 to visit 2 (i.e., across the first semester of college).

Aim 5: Test whether the change in diet quality from visit 1 to visit 2 predicts circulating cytokines, *ex vivo* stimulated cytokine production, depressive symptoms, and MetS symptom severity at visit 2.

Figure 1: Conceptual Model



Chapter 2: Literature Review

Metabolic Syndrome

Metabolic Syndrome: Definition and Public Health Relevance

MetS has been clinically defined as the concurrent presence of at least three of the following factors: abdominal obesity, elevated fasting glucose, hypertension, high triglycerides, and low HDL-C (Cornier et al., 2008; Eckel et al., 2005). In the United States, MetS prevalence is estimated at 38.3% among adults age ≥20 years (Liang et al., 2021); within the country, prevalence varies across geographic regions from a minimum of 29% to over 40% (Gurka et al., 2018). By college age, MetS symptoms are common: 58% of female and 60% of male first-year students have at least one MetS risk factor, and 2.4 to 3.2% meet full diagnostic criteria, respectively (Higgins et al., 2020). These numbers may increase across time in college, as a study including college students across all academic years found that 6.8% of students met MetS diagnostic criteria (Dalleck & Kjelland, 2012). The etiology of MetS is still being delineated; still, measurement of MetS symptoms in research is useful because it represents a practical means of identifying individuals at risk of developing CVD and/or T2D (Alberti et al., 2004). Given that CVD and T2D have closely related pathological mechanisms and are commonly comorbid (Schernthaner et al., 2018), having a set of risk factors that predicts both is pertinent. To accommodate the need for practical, universally applicable measures of disease risk, direct assessments of insulin resistance and inflammation are not included in the diagnostic criteria, despite the fact that these are considered important physiological mechanisms linking MetS to long-term disease risk (Després, 2012). Indeed, MetS is commonly considered a chronic low-grade inflammatory condition (Das, 2010; Sharma, 2011), and the combination of fasting glucose and triglyceride levels can be interpreted as an indirect measure of insulin resistance (Simental-Mendía et al., 2008).

Each component of MetS is itself an independent predictor of cardiometabolic disease; when present together, the components work synergistically to substantially increase disease

risk (Papakonstantinou et al., 2013). Indeed, the presence of MetS is associated with a 2-fold increase in CVD risk, and a 5-fold increase in T2D risk (Cornier et al., 2008). The predominant driving physiological mechanisms linking MetS to cardiometabolic disease development are abdominal obesity, insulin resistance, and chronic inflammation (Cornier et al., 2008; Després et al., 2008). However, the clustering of MetS symptoms is largely thought to be a product of over-nutrition (i.e., consuming more calories than are expended in a day) and sedentary lifestyle (Cornier et al., 2008; Després, 2012), both of which are amenable to change via intervention. Beyond its associations with physical health outcomes, MetS has also been shown to have a bidirectional association with depression (Pan et al., 2012), possibly due to the role of inflammation in the etiology of both MetS and depression (Capuron et al., 2008). Thus, interventions aimed at reducing MetS and its components could have widespread impacts on both mental and physical health outcomes.

Brief History of Metabolic Syndrome Research

Nearly a century of research has investigated the construct of MetS under various names, including [Metabolic] Syndrome X (e.g., Cannon et al., 1992) and the Insulin Resistance Syndrome (e.g., Haffner et al., 1992). The earliest research regarding what is now considered MetS was published in 1923 by the Swedish physician Eskil Kylin, who identified the common clustering of hypertension, hyperglycemia (i.e., elevated fasting glucose), and gout in his patients (Kylin, 1923). The next major advance in MetS research came in the 1940's, when the French physician Jean Vague began publishing studies on the relationship between android (i.e., abdominal) obesity and metabolic abnormalities associated with risk of CVD and T2D (Vague, 1947). The 1980's brought several major advances to the study of MetS. First, Ruderman and colleagues identified the existence of a subgroup of individuals who were in a healthy weight range, but exhibited metabolic disturbances similar to those seen in obesity, describing the phenomenon as 'metabolic obesity' (Ruderman et al., 1981). Around the same time, Gerald Reaven posited the concept of insulin resistance and described it as being central

to various pathologies (Reaven, 1988). While insulin resistance is still widely accepted as an important aspect of MetS and cardiometabolic disease pathology, the line of research inspired by Reaven's hypothesis that insulin resistance is the primary driver of MetS while obesity is relatively unimportant, remains controversial. A competing hypothesis, proposed by Lemieux and colleagues, has increased abdominal obesity and the 'hypertriglyceridaemic waist phenotype' (i.e., high levels of triglycerides in and released by excessive abdominal adipose tissue) as the driving mechanisms behind MetS and associated diseases, with insulin resistance being an effect of abdominal obesity (Lemieux et al., 2000). In addition to ongoing controversy surrounding the predominant disease mechanisms, this line of research has long been impeded by inconsistencies in how MetS is operationally defined (Eckel et al., 2005). The World Health Organization published the first finalized set of diagnostic criteria in 1999 (World Health Organization, 1999), and to date there are at least 6 clinical definitions of MetS in use. The ATP-III (NCEP Expert Panel, 2002; Grundy et al., 2019) criteria is among the most commonly used definitions (see Table 1 for detailed diagnostic criteria).

In American samples, the ATP-III and International Diabetes Federation (IDF; Alberti et al., 2009) MetS diagnostic criteria have high concordance, such that the same individual is likely to either meet or not meet diagnostic criteria regardless of which is used. Concordance between ATP-III and IDF criteria ranged from 82% to ≥92% depending upon the demographic category; while MetS prevalence was slightly higher across all 6 demographic categories using the IDF criteria, the difference was only significant for Hispanic men (Assmann et al., 2007). Some evidence suggests that, despite the high concordance, ATP-III criteria may be a stronger predictor of 10-year disease risk (Assmann et al., 2007). For example, MetS prevalence was 3.1–11.7% higher using the IDF compared to the ATP-III criteria in a sample of Austrian adults, however, individuals identified using IDF but not ATP-III criteria were found to have significantly lower concurrent insulin resistance, carotid artery intima media thickness, and arterial plaque extent (indicating lower cardiometabolic disease risk) compared to those who were identified by

ATP-III criteria (Sandhofer et al., 2007). Similarly, an 11-year study of non-diabetic patients found that MetS prevalence was higher when using IDF criteria compared to ATP-III criteria (Nilsson et al., 2007). Compared to those who did not meet MetS criteria, meeting IDF criteria was associated with an 11% increase in odds of a cardiovascular event (e.g., myocardial infarction, stroke), while meeting the ATP-III criteria was associated with a 59% increase in odds (Nilsson et al., 2007). Thus, it is possible that the IDF criteria may be too broad, and may include individuals with levels of physiological dysfunction too low to yield clinically significant adverse effects. Due to the relatively improved predictive value, the proposed study will use ATP-III criteria for MetS.

Table 1: National Cholesterol Education Program Adult Treatment Panel III (ATP-III) Metabolic Syndrome (MetS) Diagnostic Criteria

Risk Factor	Cut off for MetS
Waist circumference	
Male	≥ 102 cm (40”)
Female	≥ 88 cm (35”)
HDL cholesterol	
Male	< 40 mg/dL
Female	< 50 mg/dL
Triglyceride	≥ 150 mg/dL
Blood pressure	≥ 130/85 mmHg
Fasting Glucose	≥ 100 mg/dL

Note. MetS is defined as the presence of ≥3 criteria

Physiological Drivers of Metabolic Syndrome

While many factors contribute to MetS development, abdominal obesity is considered a primary physiological driver (Lemieux et al., 2000). Among healthy weight individuals, an elevated waist circumference (i.e., a measure of abdominal obesity) is associated with increased MetS risk (S. Chen et al., 2014), and abdominal fat mass is associated with concurrent levels of all five MetS components (Carr et al., 2004). This is especially problematic in the United States, where the prevalence of abdominal obesity has been increasing across time, alongside age-adjusted waist circumference (Ford et al., 2011). The ATP-III MetS diagnostic criteria defines abdominal obesity as a waist circumference of ≥ 102 cm for men and

≥ 88 cm for women (NCEP Expert Panel, 2002), the average waist circumference associated with an obese BMI for each sex (Lean et al., 1995). Past research has commonly used BMI to measure obesity, defined as a BMI of ≥ 30 kg/m^2 (Kopelman, 2000). However, BMI does not distinguish lean mass from fat mass, an important distinction given the different physiological properties of lean and adipose tissues (Frankenfield et al., 2001; Garn et al., 1986; Müller, 2013). A BMI = 30 kg/m^2 is associated with a body fat percentage ranging from 23 to 41% in male adults, and 30 to 51% in females (Müller et al., 2010). Among adults with a non-obese BMI (< 30 kg/m^2), 30% of males and 46% of females have a body fat percentage in the obese range (Frankenfield et al., 2001). Thus, alternative measures have been developed to identify abdominal obesity regardless of BMI status (Müller, 2013). Several such measures exist, but waist circumference is among the most practical and widely used (Ness-Abramof & Apovian, 2008).

Two distinct abdominal fat depots are included in measures of waist circumference: subcutaneous fat, which lies between the skin and the abdominal cavity, and visceral fat, which surrounds organs inside the abdominal cavity (Seidell et al., 1987). Both depots play similar roles in the development of MetS via metabolically and immunologically active secretions (Misra & Vikram, 2003), and release of free fatty acids (Bjorntorp, 1990; Z. Guo et al., 1999). Subcutaneous adipocytes are the primary means of energy storage in the body (Ebbert & Jensen, 2013). In lipogenesis, dietary glucose and fatty acids that are not immediately oxidized are absorbed by adipocytes and converted into triglycerides for energy storage (Ebbert & Jensen, 2013). Triglycerides, being too large to pass from adipocytes directly into circulation, are broken down into smaller free fatty acids by intracellular lipolysis; these free fatty acids are then released into circulation for use by bodily cells and tissues (Ebbert & Jensen, 2013). Free fatty acids can be converted back into triglycerides when bound to the glycerol 3-phosphate produced by glucose metabolism (Engin, 2017; R. H. Unger, 1995). When fat storage needs exceed the functional storage capacity of subcutaneous adipocytes, excess fatty acids and

triglycerides are deposited ectopically (i.e., in an abnormal place) as lipid droplets in other tissues and organs, including the liver, pancreas (Scheja & Heeren, 2019), kidneys (Guebre-Egziabher et al., 2013), and visceral adipose tissue (Ebbert & Jensen, 2013; Jensen, 2008). As obesity progresses, adipocytes become less able to absorb and retain fats, and release free fatty acids at a higher rate (Scheja & Heeren, 2019).

Circulating free fatty acids can be deposited ectopically in the liver and the pancreas, contributing to the development of insulin resistance and MetS in several ways. Excessive delivery of free fatty acids to the liver increases glucose and triglyceride production, potentially leading to elevated circulating glucose and triglycerides, both of which are MetS symptoms, and to non-alcoholic liver steatosis (Misra & Vikram, 2003). Notably, visceral fat depots divert excess free fatty acids directly to the portal venous system (which flows into the capillary bed of the liver), making this abdominal fat depot critically important in the maintenance or decline of liver function (Misra & Vikram, 2003). Ectopic deposits of free fatty acids and triglycerides in the liver reduce its capacity to clear circulating insulin, leading to excessive circulating insulin, and subsequently to downregulation of cellular insulin receptors and insulin resistance (Misra & Vikram, 2003). Rodent models of obesity and obesity-dependent T2D have shown that ectopic free fatty acids in the pancreas increase the concentration of triglycerides in pancreatic islets (R. H. Unger, 1995). The resulting buildup of fatty acids and triglycerides has lipotoxic effects on islet β-cells (i.e., insulin-producing cells), including increasing β-cell volume, cellular depletion, and fibrosis, analogous to non-alcoholic liver steatosis development (Engin, 2017; R. H. Unger, 1995). Cellular changes were followed by the development of insulin resistance and subsequently T2D (R. H. Unger, 1995). Thus, evidence suggests that the excessive free fatty acids generated in abdominal obesity can induce insulin resistance, another key driver of MetS etiology, at least in part by impairing function of the liver and pancreas (Misra & Vikram, 2003; R. H. Unger, 1995). Adipocyte release of free fatty acids is regulated in part by insulin; insulin

resistance thus results in higher release of free fatty acids, creating a positive feedback loop (Ebbert & Jensen, 2013).

Excessive free fatty acids also induce the liver to excrete higher levels of the highly atherogenic, triglyceride-heavy, very low-density lipoprotein cholesterol (vLDL), thus increasing circulating vLDL and triglycerides (Misra & Vikram, 2003). Cholesterol esters of circulating cardioprotective HDL-C molecules readily accept triglycerides from vLDL molecules (Mudd et al., 2007). The resulting triglyceride-rich HDL-C is broken down by hepatic lipase into smaller HDL particles that are easily excreted by the kidneys (Mudd et al., 2007). Thus, the free fatty acids produced by abdominal adipose tissue lead to insulin resistance, increasing levels of circulating triglycerides, and decreasing levels of circulating HDL-C (Misra & Vikram, 2003), thereby contributing to the development of MetS.

Direct measures of inflammation are not included in the definition of MetS due to their cost and complexity; however, chronic inflammation is considered a predominant mechanism in MetS etiology (Welty et al., 2016). Development of chronic inflammation, in this case, also involves abdominal adipose tissue (Elks & Francis, 2010). Adipocytes modulate innate immunity, metabolism, and insulin sensitivity via secretion of hormones and cytokines (Hassan et al., 2012). Adipocytes express receptors for a diverse array of pro-inflammatory cytokines, including TNF-1A, TNF-1B, and toll-like receptor 4 (TLR4), and thus can activate the nuclear factor (NF)-κB signal transduction pathway (Berg et al., 2004). Stimulation of adipocytes by IL-1β, IL-4, IL-6, IL-11 or interferon (IFN)-γ can activate pro-inflammatory cascades with organism-wide effects; stimulated adipocytes can also directly secrete IL-1β, IL-6, IL-8, IL-10, IL-15, and TNFs, among other cytokines and hormones (Hassan et al., 2012). Past research has identified secretion of IL-6 by abdominal adipose tissue and subsequent inflammatory pathway activation as a key mechanism linking abdominal obesity to chronic inflammation and long-term disease risk (Fontana et al., 2007). Obesity and insulin resistance are each also associated with increased Nucleotide-binding Oligomerization Domain (NOD)-like receptor pyrin domain–

containing-3 (NLRP3) inflammasome expression in adipose tissue (Rheinheimer et al., 2017; Vandanmagsar et al., 2011). The visceral adipose tissue of obese individuals with MetS produce IL-1β at a rate four times higher than that of metabolically healthy obese individuals (Esser et al., 2013). Given that IL-1β is an activator of the NLRP3 inflammasome, this represents a plausible mechanism linking abdominal obesity, inflammation, and MetS development. Inflammatory pathways and cytokines are discussed in depth in Chapter 2.2.

Adipose tissue resident immune cells also have important physiological functions: in lean individuals, these cells are involved in the maintenance of adipose tissue, including apoptotic cell clearance, extracellular matrix remodeling, and maintaining insulin sensitivity (Schipper et al., 2012). As obesity progresses, abdominal adipose tissue secretes more pro-inflammatory compounds in a way that mimics the effects of bacterial infection, thereby activating adipose tissue resident immune cells and increasing recruitment of additional immune cells from circulation into adipose tissue (Schipper et al., 2012). The presence of pro-inflammatory cytokines in adipose tissue triggers the activation of macrophages into their pro-inflammatory M1 polarization phenotype (O'Sullivan et al., 2016). M1 macrophages secrete TNF-α, IL-1β, and IL-6, directly contributing to the development of insulin resistance (Olefsky & Glass, 2010). Insulin resistance contributes to even higher levels of adipose tissue dysfunction and the development of chronic low-grade inflammation (Schipper et al., 2012).

Abdominal adipose tissue may be especially prone to this type of dysregulation due to the high proportion of resident immune cells: even in healthy weight individuals, visceral adipose tissue contains twice as many macrophages as adipose tissue elsewhere (Kralova Lesna et al., 2016). The proportion of immune cells increases with increasing BMI, suggesting immune cells are recruited at a higher rate as abdominal fat tissue grows (Curat et al., 2004). Research using rodent models has found that resident adipose tissue macrophages (i.e., macrophages that have migrated into abdominal tissue) represent over 50% of the cells in adipose tissue in obese animals, compared to just 5-10% of the cells in adipose tissue in lean animals (Weisberg et al.,

2003). In addition, abdominal tissue resident macrophages in obese individuals with MetS show increased IL-1β secretion in response to incubation with a fluorogenic caspase-1 substrate compared to both metabolically healthy obese individuals and healthy weight individuals (Esser et al., 2013), suggesting that MetS is associated with heightened pro-inflammatory activity in response to *ex vivo* stimulation. Indeed, site-specific dysregulation of adipose tissue and resulting increases in inflammation are considered major factors in the development of MetS and associated diseases (Phillips & Prins, 2008).

Inflammation

The innate immune system is a highly conserved protective mechanism present in most multicellular organisms, and is responsible for recognizing and responding to host infection or injury (Medzhitov & Janeway, 2000). The innate immune system has wide-ranging functions, including responding to infection or injury via an acute inflammatory response (e.g., Rankin, 2004). Phagocytic immune cells, such as neutrophils and macrophages, are generally among the first to detect injury or infection; binding of molecular distress signals activates these cells, initiating secretion of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-8 (Cross & Opal, 2003; Kumar et al., 2004), as well as anti-inflammatory cytokines, such as IL-10 (Kumar et al., 2004). The presence of pro-inflammatory cytokines attracts additional immune cells to the area, increases local blood flow, and increases the permeability of capillary walls (Rankin, 2004) Immune cells can then migrate from circulation, through the capillary walls, and into interstitial space in the injured or infected tissue, in a process known as diapedesis (Rankin, 2004). Once in the tissue, phagocytic immune cells engulf infecting bacterial cells or dysfunctional host cells and kill them by secreting toxic compounds (e.g., oxygen free radicals) (Janeway et al., 2001). Ideally, this results in the threat being eliminated, allowing a return to homeostasis through anti-inflammatory cascades within a short period of time, typically hours to days (Kumar et al., 2004). However, under some circumstances, acute inflammation goes unresolved and becomes chronic inflammation (e.g., Lickorish et al., 2004).

Transition from Acute to Chronic Inflammation

The pathway from acute to chronic inflammation is still being delineated; however, some general causes of chronic inflammation have been identified (Pahwa et al., 2014; Soehnlein et al., 2017). Broadly, the two main reasons that acute inflammation becomes chronic are either 1) the stimulus that initiated inflammation cannot be cleared, or 2) a resolution response is not successfully generated (Lawrence & Gilroy, 2007; Soehnlein et al., 2017). Consistent exposure to pro-inflammatory irritants, such as environmental pollution or a poor-quality diet, represents a category of stimuli that cannot easily be cleared. Because hyperlipidemia and hyperglycemia are also considered pro-inflammatory (Soehnlein et al., 2017), the elevated triglycerides and glucose seen in MetS could also be considered irritants that cannot be cleared. Inflammation can fail to resolve due to the initiation of a self-perpetuating cycle in which pro-inflammatory cytokines induce oxidative stress and mitochondrial dysfunction, thereby increasing production of free radicals, advanced glycation end products (AGEs), and other compounds that stimulate further inflammation. Intriguingly, acute stress also stimulates a pro-inflammatory response, which is generally downregulated by cortisol, a glucocorticoid that is the end product of the human endocrine stress response system (Rohleder, 2019; Steptoe et al., 2001; Yamakawa et al., 2009). Chronic stress is also associated with chronic inflammation, possibly due to the development of glucocorticoid resistance (Barnes & Adcock, 2009; G. E. Miller et al., 2002; Pace et al., 2007; Sapolsky et al., 2000). In glucocorticoid resistance, excessive exposure to glucocorticoids results in immune cell glucocorticoid receptors becoming progressively less sensitive, impairing anti-inflammatory signaling and resulting in prolonged inflammation (Cohen et al., 2012). Across time, chronic stress and associated glucocorticoid dysregulation can contribute to increasing glucocorticoid resistance, in turn promoting the development of chronic inflammation (Cohen et al., 2012). Development of chronic inflammation is hypothesized to be an important mechanism linking chronic stress to MetS and associated cardiometabolic diseases (Rohleder, 2014; Segerstrom & Miller, 2004).

Threat Detection

Immune cells express pattern recognition receptors (PRRs) that recognize molecular signals indicative of infection or damage; when a signaling ligand binds to one of these receptors, an acute inflammatory response is initiated to destroy the infecting pathogens and/or repair damage (Medzhitov & Janeway, 2002; Takeuchi & Akira, 2010). There are two broad families of PRRs: 1) transmembrane proteins, such as TLRs, are components of the cell membrane; while 2) cytoplasmic proteins, such as NLRs, are found within the cytoplasm (Kumar et al., 2011; Takeuchi & Akira, 2010). All immune cells express PRRs, as do other 'nonprofessional' immune cells, such as intestinal stromal cells, adipocytes, endothelial cells, and epithelial cells, allowing these cells to transmit information about infection or damage to professional immune cells (Hamada et al., 2019). Immune cells are able to detect and react to three basic categories of molecular pattern: microbial non-self, missing-self, and induced or altered self (Medzhitov & Janeway, 2002).

Detection of microbial non-self relies on pathogen-associated molecular patterns (PAMPs), conserved molecular products generated by normal physiological processes in any microbe, whether or not the microbe is truly pathogenic (Medzhitov & Janeway, 1997, 2002). PAMPs are unique to microbes and are not produced by the host animal; additionally, any microbe within a given class produces the same PAMPs. Thus, PAMPs are unique molecular signatures used by the innate immune system to identify microbial infection (Medzhitov & Janeway, 1997, 2002). While a full review of PAMPs and their associated microbes is beyond the scope of this review, LPS from gram-negative bacteria is among the most widely studied PAMPs (Medzhitov & Janeway, 2002).

Missing-self is recognized by the absence of components that should be present in host cells (Kärre et al., 1986; Medzhitov & Janeway, 2002). This form of recognition was first characterized in natural killer (NK) cells that sense the absence or reduced expression of major histocompatibility complex class 1 (MHC-1), (Zinkernagel & Doherty, 1975). MHC-1 is an

antigen-presenting surface protein found in the nucleated cells of all vertebrates, including most healthy human cells (Wieczorek et al., 2017). Constitutive production (i.e., continuous production as part of normal cell function) of MHC-1 is downregulated by viral infection and adverse cellular transformations, and thus low MHC-1 could indicate an infected or dysfunctional cell (Kärre et al., 1986; Zinkernagel & Doherty, 1975). Other forms of missing-self recognition based off the principle of identifying the absence of expected components of human cells have also been delineated, such as regulation of the alternative complement pathway (Austen & Fearon, 1979).

Induced or altered self is recognized via damage associated molecular patterns (DAMPs) produced by host cells (Matzinger, 1994). Under normal circumstances, DAMPs fulfill physiological functions inside host cells, where they are invisible to the innate immune system (Bianchi, 2007; Vénéreau et al., 2015). However, under conditions of cellular damage or physiological stress, DAMPs leak out of, or are secreted by, the cell into surrounding fluids where they can be recognized by immune cells to alert the body of damage, initiate an inflammatory response, and encourage regeneration (Bianchi, 2007; Vénéreau et al., 2015). Adenosine tri-phosphate (ATP) is an exemplary DAMP; within a cell, ATP is used as a source of energy (Boyer, 1998). However, once outside the cell, such as when secreted by an apoptotic (i.e., dying) cell, ATP acts as a signal to macrophages, binding to P2Y2 receptors (a type of PRR) and initiating phagocytosis of the dying cell (Idzko et al., 2014; Kouzaki et al., 2011). Generally, extracellular ATP is quickly decomposed into adenosine, thereby limiting the amount of time that the pro-inflammatory reaction can occur (i.e., acute inflammation; Vénéreau et al., 2015). In some conditions, such as pneumonia (Idzko et al., 2014) and allergies (Kouzaki et al., 2011), ATP-driven activation of P2Y2 receptors has been shown to induce chronic inflammation.

Key Inflammatory Pathway 1: NLRP3 Inflammasome

Inflammasomes are multiprotein intracellular complexes that mediate production of the pro-inflammatory cytokines IL-1β and IL-18 by activating caspase-1 in response to detection of

DAMPs or PAMPs (Franchi et al., 2009). NLRs, a family of cytoplasmic PRRs, bind biochemical threat signals, initiating activation of caspase-1, and subsequently activating the inflammasome (Franchi et al., 2009; Martinon & Tschopp, 2004). The inactive procaspase-1 zymogen, present in the cytoplasm of phagocytic cells, self-cleaves upon activation by NLRs (Cerretti et al., 1992; Thornberry et al., 1992). Once activated, caspase-1 enzymatically cleaves pro–interleukin 1β and pro-IL-18 precursors to yield active IL-1β and IL-18 (Franchi et al., 2009; Martinon & Tschopp, 2004). Active IL-1β is involved in a wide range of pro-inflammatory actions, including the recruitment of additional immune cells (Martinon & Tschopp, 2004) and stimulating production of IL-6 (Liu et al., 2015). IL-18, previously known as IFN-γ inducing factor, also has several pro-inflammatory actions, including inducing production of IFN-γ (Ushio et al., 1996) and TNF-α (Gracie et al., 1999), as well as modulating activity of immune cells, including T cells, B cells, NK cells, and macrophages (Dinarello, 2007).

While several NLR inflammasome families exist, the NLRP3 inflammasome is of particular interest here due to its established associations with MetS (Jialal et al., 2021; Pahwa, et al., 2021; Wani et al., 2021). In abdominal obesity, a central symptom of MetS (Lemieux et al., 2000), abdominal adipose tissue becomes increasingly dysfunctional, resulting in the activation of adipose tissue macrophages from the anti-inflammatory M2 to the pro-inflammatory M1 type (Castoldi et al., 2016). Interactions between M1 macrophages and adipocytes, including via secreted pro-inflammatory cytokines, result in metabolic stress and the production of DAMPs by adipocytes (Wani et al., 2021). NLRP3 is somewhat unique in that, while many PRRs recognize only a small number of stimulating factors, NLRP3 recognizes a wide range of endogenous molecules and environmental irritants that lead to physiological distress at a cellular level (Swanson et al., 2019). The metabolic distress signals produced by dysfunctional adipocytes are recognized by NLRP3, leading to activation of the inflammasome (Barra et al., 2020; Schroder et al., 2010). Activation of the NLRP3 inflammasome results in increased production of pro-inflammatory cytokines and increased recruitment of macrophages, yielding a

self-perpetuating cycle of adipocyte dysfunction and inflammasome activation, thereby contributing to the development of chronic inflammation and MetS (Ozaki et al., 2015).

Activation of the NLRP3 inflammasome is a two-step process (Broz & Dixit, 2016). The first step is priming, in which detection of either endogenous cytokines (e.g., TNF-α or IL-1β) or PAMPs (e.g., LPS) upregulates production of components necessary for inflammasome activation, including production of NLRP3 protein, pro-IL-1β and pro-IL-18, mediated by NF-κB transcription factors (Bauernfeind et al., 2009; Yamamoto & Gaynor, 2005). In step 2, detection of DAMPs and PAMPs stimulates inactive NLRP3 proteins in the cytoplasm to assemble into an oligomer, leading to the self-cleaving of pro-caspase-1 into caspase-1 through as yet undefined mechanisms (Swanson et al., 2019; Wani et al., 2021). In MetS, specifically, the metabolites isoleucine, γ-aminobutyric acid (GABA), carnitine, and phosphatidylcholine 34:2 may act as NLRP3-stimulating DAMPs (Jialal et al., 2021).

Key Inflammatory Pathway 2: TLR4 / NF- κβ Pathway

While a wide range of inflammatory pathways and cytokines have been identified, much of the existing knowledge about inflammation comes from the study of the IL-1 family of cytokines and associated IL-1 family receptors, called TLRs (Loiarro et al., 2010). At least 12 TLRs have been identified in mammals (Akira et al., 2006). Of these, TLR4 is most applicable here due its central role in diet- (Kim et al., 2014) and obesity-induced inflammation (H. Shi et al., 2006; Suganami et al., 2007). TLR4 recognizes LPS from gram-negative bacteria, such as *Bacteroides* in the intestinal microbiome (Kim et al., 2014; Poltorak et al., 1998), as well as circulating nutritional lipids, such as high- and low- density lipoprotein cholesterol (H. Shi et al., 2006). LPS directly binds to CD14 or LPS binding protein; however, because CD14 is a surface receptor, it cannot transduce signals across the membrane (Chow et al., 1999). Instead, upon binding LPS, the CD14/LPS complex binds to TLR4 (Chow et al., 1999). Binding of CD14/LPS activates TLR4, which in turn leads to activation of NF-κB (Chow et al., 1999). Activation of NF-

κB stimulates synthesis of several pro-inflammatory cytokines, including IL-1, IL-6, IL-8, and TNF-α (Chow et al., 1999).

In mice, high-fat diet has been shown to increase both adiposity and circulating levels of LPS, a condition called endotoxemia, sufficiently to increase body weight, fasting glucose, and inflammatory markers (Cani et al., 2007). Intriguingly, the microbiome of these mice was also found to have a lower proportion of *Bacteroides*-like mouse intestinal bacteria, which are gram-negative, LPS-containing microbes (Cani et al., 2007). The precise mechanisms by which this occurs remain unclear; however, research using mouse models has found that intestinal epithelial cells absorb LPS through their apical surface and transport it to the Golgi apparatus, an organelle responsible for packaging proteins into chylomicrons for secretion (Ghoshal et al., 2009). Chylomicrons express LPS binding proteins on their surface, and consequently have an affinity for LPS (Ghoshal et al., 2009; Vreugdenhil et al., 2003). Thus, LPS absorbed via intestinal immune cells gets packaged by the Golgi into chylomicrons, and then secreted into circulation (Ghoshal et al., 2009). It is plausible that a similar mechanism may be at play in the increased circulating LPS seen with exposure to high-fat diet (Cani et al., 2007). Circulating chylomicrons can present bound LPS to TLR4-expressing macrophages, initiating an inflammatory cascade. Whether diet-related increases in circulating LPS and associated increases in TLR4 expression can yield chronic inflammation remains subject to debate, and additional research is needed to clarify this potential mechanism (Hollander & Kaunitz, 2020).

Circulating Makers of Inflammation

Development of chronic inflammation both precedes and actively participates in the development of many adverse health conditions, including MetS, CVD, T2D, and MDD (Kiecolt-Glaser et al., 2015; Manabe, 2011; Prasad et al., 2012). As such, a vast body of research has been produced attempting to leverage circulating markers of inflammation for prevention research. While measures of *in vivo* circulating inflammatory markers contain valuable information, this line of research is limited by floor effects (Kleiner et al., 2013; Zhou et al.,

2010). In young and/or healthy (i.e., free of chronic disease) individuals, circulating inflammatory markers often fall below the level of measurable detection (Kleiner et al., 2013; Zhou et al., 2010). Consequently, this measure may not be a reliable indicator of inflammation-related disease risk in younger, healthier samples such as first year college students. To design effective prevention programs for inflammation-related diseases, a measure of inflammatory capacity suitable for use in young, healthy subjects, prior to disease onset, is needed.

Ex Vivo-Stimulated Cytokine Production

Inflammation can be measured using *ex vivo* stimulation of whole blood samples with an antigen, most commonly LPS (Rossol et al., 2011). While *ex vivo* immune responses may not be identical to *in vivo* responses (Kox et al., 2011), the mechanisms by which LPS induces inflammation are similar in both circumstances. LPS can initiate both priming and activation of the NLRP3 inflammasome, (Kelley et al., 2019; Swanson et al., 2019); activation of the NLRP3 inflammasome results in the production of IL-1β and IL-18 (Franchi et al., 2009; Martinon & Tschopp, 2004). In addition, LPS binds to TLR4, activating the NF-κB pathway, and leading to the production of pro-inflammatory cytokines including IL-1, IL-6, IL-8, and TNF-α (Chow et al., 1999; Schletter et al., 1995). Given that TLR4 expression has been implicated in the development of MetS (Jialal et al., 2021; Jialal et al., 2012), CVD (Kim et al., 2007), T2D (Taha et al., 2018), and MDD (Liu et al., 2014; Wu et al., 2015), LPS-induced inflammatory responses represent an exciting means of examining a potential common disease mechanism. Further, because the NLRP3 inflammasome is activated in dysfunctional adipocytes in MetS (Jialal et al., 2021; Pahwa, et al. 2021), and the TLR4/ NF-κB pathway is involved in inflammation caused by poor diet quality (Kim et al., 2014; Nobs et al., 2020), measurement of *ex vivo* LPS-stimulated inflammation may be a valid proxy measure of the pro-inflammatory process associated with poor diet quality and the development of MetS.

Individual differences in the magnitude of the *ex vivo* inflammatory response to LPS are thought to reflect individual differences in inflammation-related disease risk. For example, whole

blood samples taken from individuals with high blood pressure, a MetS component and CVD risk factor, have been shown to exhibit increased IL-1 and IL-6 production in response to *ex vivo* LPS stimulation compared to blood samples taken from healthy individuals (Peeters et al., 2001). Past research has found that modulation by specific nutrients (discussed in Chapter 2.3) leads to alterations in *ex vivo* LPS-stimulated inflammation (Koutsos et al., 2014). However, to date no published studies have examined the impact of overall diet quality on *ex vivo* LPS-stimulated inflammation in humans. Thus, *ex vivo* LPS-stimulated inflammation represents a promising but underused measure in diet-related human subjects research.

Diet Quality

Poor diet quality has been implicated in the development of a wide range of adverse health outcomes, including MetS (Giugliano et al., 2006; Riccardi & Rivellese, 2000), obesity (Asghari et al., 2017), CVD (Bowen et al., 2018; Van Horn et al., 2008), T2D (Neuenschwander et al., 2019), and MDD (Lassale et al., 2019; Molendijk et al., 2018). Suboptimal diet is considered the leading modifiable contributor to disease risk, contributing to approximately 529,299 deaths in 2016 alone (Murray et al., 2018). Indeed, 45.4% of cardiovascular and metabolic disease mortalities can be attributed to poor diet quality (Benjamin et al., 2019). Despite the strong and substantial evidence linking diet quality and health, only 0.2% of American adults currently consume an optimal diet (Kris-Etherton et al., 2020), while 82% of adults aged 20-49 years currently consume a poor quality diet (Benjamin et al., 2019). While there are several definitions of an optimal diet, common factors include high consumption of fruits, vegetables, and whole grains, alongside low consumption of sodium, added sugars, saturated fats, and refined grains (Benjamin et al., 2019; Krebs-Smith et al., 2018).

Diet Quality and Metabolic Syndrome

The prevalence of poor diet quality has implications for MetS research, as individuals in the highest adherence to the Western dietary pattern (i.e., the lowest-quality diet) are 128% more likely to have MetS compared to those with better diet quality (Osadnik et al., 2020).

Conversely, a healthy diet has protective effects: being in the highest quartile for diet quality is associated with a 35% reduction in odds of concurrent MetS compared to the lowest quartile (Nicklas et al., 2012). Rodent models have demonstrated that a modified high-fat/high-carb diet can independently induce MetS (Sok Kuan Wong et al., 2018), and a promising line of research to standardize rodent models of diet-induced MetS is ongoing (Leonardi et al., 2020). Importantly, rodent models have also shown that it is possible to prevent and reverse symptoms of MetS via dietary changes (Bolsinger et al., 2017; Parekh et al., 1998); suggesting that dietary changes could also be used to reduce MetS in humans (Andersen & Fernandez, 2013).

A vast body of research supports the association between diet quality and health outcomes. For example, the average Western diet is high in saturated fats, added sugars, and processed foods, and low in fiber; this dietary pattern contributes to the development of chronic inflammation (Christ et al., 2018; Nobs et al., 2020), thereby contributing to the development of MetS (Das, 2010; Drake et al., 2018) and eventually CVD and T2D (Stanhope et al., 2018). Individuals in the highest quintile for adherence to a Western dietary pattern have an 18% increase in risk of MetS development across a 9-year follow up period compared to the lowest quintile (Lutsey et al., 2008). Meat, fried food, and diet soda consumption were the specific food items that independently increased MetS risk, while dairy consumption was found to be protective (Lutsey et al., 2008). Consumption of fructose, a simple sugar often consumed in table sugar or high-fructose corn syrup, has also been associated with the development of most MetS symptoms, including elevated fasting glucose, reduced HDL-C, and elevated blood pressure (Jameel et al., 2014; Kelishadi et al., 2014).

Conversely, adherence to a healthy dietary pattern, such as the Mediterranean dietary pattern (Keys, 1970), is associated with attenuated MetS risk (Babio et al., 2009; Godos et al., 2017), possibly due to associated decreases in pro-inflammatory activity (Nobs et al., 2020). The Mediterranean diet is also associated with reduced MetS symptoms, including lower concurrent waist circumference and a lower rate of increase in waist circumference across 10

years (Funtikova et al., 2014), as well as improved insulin sensitivity, improved blood lipid profiles, reduced blood pressure, and reduced inflammation (Babio et al., 2009; Esposito et al., 2013; Giugliano et al., 2006). Adherence to the Mediterranean diet has also been shown to attenuate the adverse physiological outcomes associated with abdominal obesity (Eguaras et al., 2015). The Prevention with Mediterranean Diet (PREDIMED) study, a large randomized control trial designed to assess the health effects of following the Mediterranean diet pattern in high-risk but disease-free individuals, found that abdominal obesity at baseline was associated with cardiovascular morbidity and mortality in the control group, but this association was not significant for the group randomized to the Mediterranean diet intervention (Eguaras et al., 2015). Consuming a healthy diet therefore represents a practical means of intervening to both reduce waist circumference and attenuate the adverse health outcomes associated with abdominal obesity, such as MetS.

Healthy Eating Index

The Healthy Eating Index (HEI) is a measure of adherence to the Dietary Guidelines for Americans; versions of the HEI have been used as a measure of diet quality in over 300 publications (Schap et al., 2017). While the US Department of Agriculture has been issuing dietary recommendations since 1894, the first edition of the Dietary Guidelines for Americans (DGA) was published in 1980 (Jahns et al., 2018). The first move to base these guidelines on accumulated scientific evidence didn't occur until 1984, when the independent U.S. Preventive Services Task Force was introduced; the evidence-based approach gained popularity in the 1990's and led to the development of progressively more detailed guidelines (Watts et al., 2011). DGA guidelines are reviewed and updated every 5 years, with the most recent edition covering 2020-2025 (U.S. Department of Agriculture and U.S. Department of Health and Human Services & U.S. Department of Agriculture and U.S. Department of Health and Human Services., 2020); consequently, several versions of the HEI have been published, as it has consistently been updated to match changes to the DGA.

The first HEI was published in 1995 and was based off the DGA 1990-1995 (Kennedy et al., 1995). Beginning in 2005, new versions of the HEI have been density-based, expressing consumption of dietary components per 1000 calories, and thus allowing assessment of diet quality independent of quantity (Guenther et al., 2008; Krebs-Smith et al., 2018). Because the HEI has not yet been updated for the DGA 2020-2025, the most recent edition is the HEI-2015, based off the DGA 2015-2020 (Krebs-Smith et al., 2018). Please see Table 2 for a detailed explanation of HEI-2015 components. The HEI-2015 assesses 13 diet components; there are 9 adequacy components, in which higher consumption is generally better, including: total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids. There are also four moderation components, in which lower consumption is generally better, including: refined grains, sodium, added sugars, and saturated fats (Krebs-Smith et al., 2018). Each component is worth either 5 or 10 points, with the moderation components being reverse scored such that higher scores indicate a healthier level of consumption for each component (Krebs-Smith et al., 2018; Reedy et al., 2018). The maximum score, indicating an optimum diet, is 100 (Krebs-Smith et al., 2018). Past research has supported the construct validity, reliability, and criterion validity of the HEI-2015 (Reedy et al., 2018).

Despite the widespread use of the HEI and the known relationship between diet quality and MetS, surprisingly few studies have directly examined associations between scores on recent HEI versions and MetS risk. One cross-sectional study found that women in the highest quartile of HEI-2010 scores were 28% less likely to have MetS; most MetS symptoms, including abdominal obesity, blood pressure, triglycerides, and HDL-C significantly improved with increasing HEI-2010 quartiles (Saraf-Bank et al., 2017). A second cross-sectional study of obese but otherwise healthy adults also found that HEI-2015 scores were significantly associated with risk of MetS, and that HEI scores mediated the association between socio-demographic variables and the presence of MetS components (Khodarahmi et al., 2019).

Table 2: Healthy Eating Index 2015 Components

Component	Points Possible	Criteria for Minimum Score	Criteria for Maximum Score
Adequacy Components (more is generally better)			
Total fruits	0-5	No fruit	≥0.8 cup equivalents[ǂ]
Whole fruits	0-5	No whole fruit	≥0.4 cup equivalents[ǂ]
Total vegetables	0-5	No vegetables	≥1.1 cup equivalents[ǂ]
Greens and beans	0-5	No dark green vegetables or beans/peas	≥0.2 cup equivalents[ǂ]
Whole grains	0-10	No whole grains	≥1.5 oz equivalents[ǂ]
Dairy	0-10	No dairy	≥1.3 cup equivalents[ǂ]
Total protein	0-5	No protein foods	≥2.5 cup equivalents[ǂ]
Seafood and plant protein	0-5	No seafood or plant proteins	≥0.8 cup equivalents[ǂ]
Fatty acid ratio[ŧ]	0-10	(PUFA + MUFA) / SFA ≤ 1.2	(PUFA + MUFA) / SFA ≥ 2.5
Moderation Components (less is generally better)			
Refined grains	0-10	≥4.3 oz equivalents[ǂ]	≤1.8 oz equivalents[ǂ]
Sodium	0-10	≥2.0g [ǂ]	≤1.1g[ǂ]
Added sugars	0-10	≥26% of total energy	≤6.5% of total energy
Saturated fat	0-10	≥16% of total energy	≤8% of total energy

Note. MUFA, Monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; [ŧ]the fatty acid ratio reflects the ratio of unsaturated (i.e., healthy) to saturated (i.e., unhealthy) fatty acids in the diet; [ǂ]per 1000 kilocalories

Diet and Inflammation

Diet may impact the development of such a broad base of diseases through the regulation of inflammatory processes by consumed nutrients (Chandra, 1997; Nobs et al., 2020; Wan et al., 1989). Both under- and over-nutrition (i.e., eating too little or too much relative to the body's needs) can substantially impair immune function and result in adverse pro-inflammatory effects (Chandra, 1997; Chandra & Kumari, 1994). Direct interaction between cells of the innate immune system and nutrients occurs primarily at the intestinal mucosal barrier, and involves two main inflammatory pathways: 1. The TLR4/NF-κB signaling pathway (Kim et al., 2012; Shi et al., 2006); and 2. The NLRP3 inflammasome (Yang et al., 2019). For an in-depth exploration of these inflammatory pathways, please see Chapter 2.2. Briefly, the NLRP3 inflammasome and TLR4 pathway can be conceptualized as two sensors of innate immune system; when these sensors are activated, pro-inflammatory cytokines are produced, and immune cells are activated

in an attempt to seek out and destroy the source of activation. Consistent activation of the NLRP3 inflammasome is involved in the development of insulin resistance (Rheinheimer et al., 2017; Vandanmagsar et al., 2011), a driver of MetS pathophysiology (McCracken et al., 2018; Reaven, 1988).

While additional research is needed, the literature generally supports sugar intake and dietary fatty acid composition as key players in diet-induced inflammation and MetS development (Calder, 2002, 2006; Giugliano et al., 2006; Nobs et al., 2020). However, because individual dietary components do not act in isolation, emphasis in research is increasingly placed on the associations between dietary patterns and associated health risks (Cespedes & Hu, 2015). Despite this trend, little research has directly assessed associations between HEI scores and markers of inflammation. One study found no relationship between HEI score and markers of inflammation (Fung et al., 2005); however, several significant findings have been reported. In a study examining 13,811 National Health and Nutrition Examination Survey III (NHANES-III) participants, each 10 point (i.e., 10%) increase in HEI score was associated with a 92% increase in odds of having elevated CRP (≥ 85th percentile); further analysis found grains to be the only specific food group significantly associated with CRP concentration (Ford et al., 2005). The association between grain consumption and CRP was negative, implying anti-inflammatory properties (Ford et al., 2005), despite the fact that the original HEI grains category did not yet distinguish between whole and refined grains (Kennedy et al., 1995; Welsh et al., 1992). An inverse association between HEI-2015 (adapted for Brazilians) scores and CRP was also found in a sample of pre-diabetic adults (Monfort-Pires et al., 2014). Similarly, a significant inverse association was found between HEI-2015 scores and levels of CRP and IL-6 in a sample of 1,989 generally healthy adults (Millar et al., 2021). Further examination of the association between HEI-2015 scores and markers of inflammation in healthy individuals is therefore warranted.

In regards to stimulated inflammation, past research using rodent (Lin & Tang, 2008; Marier et al., 2005; Qazi et al., 2009) and human (Boots et al., 2008; Damsgaard et al., 2009; Sureda et al., 2020) models has found associations between specific foods and nutrients and *ex vivo* LPS-induced inflammation. Additionally, one study found that modulation of dietary fat content led to alterations in *ex vivo* LPS stimulated inflammation in a sample of normolipidemic human adults (i.e., adults with blood lipid levels in the healthy range) (Koutsos et al., 2014). TNF-α production after a consumption of a high saturated fat diet was significantly higher compared to both baseline and a low saturated fat diet; addition of docosahexaenoic acid (DHA; an omega-3 PUFA) to the high saturated fat diet resulted in TNF-α production that was significantly higher than baseline only. Furthermore, production of IL-10, a generally anti-inflammatory cytokine, was significantly higher in the low saturated fat diet compared to baseline and the high saturated fat + DHA condition. Thus, it is plausible that dietary changes could alter immune system function and inflammatory processes.

Depression

Major depressive disorder (MDD) is the leading cause of disability worldwide (Freidrich, 2017), and the most prevalent psychological disorder experienced by college students (Brandy et al., 2015). While classic anti-depressant therapies such as Selective Serotonin Reuptake Inhibitors (SSRIs) are effective in 60 to 70% of patients, nearly a third of MDD patients are treatment resistant and do not experience a reduction in symptoms when prescribed such medications (Souery et al., 2006). MDD is also a heterogeneous disorder, with diagnostic criteria including marked changes in affect, cognition, and neurovegetative functions [i.e., appetite and sleep (Toenders et al., 2020)] lasting ≥2 weeks, as well as inter-episode remissions (American Psychatric Association, 2013).

Depression and Metabolic Syndrome

In addition to the immediate impacts on mood and function, MDD is associated with all three key physiological drivers of MetS development: abdominal obesity (Luppino et al., 2010;

Xu et al., 2011), insulin resistance (Pan et al., 2008), and chronic inflammation (Howren et al., 2009; Kiecolt-Glaser et al., 2015; Kiecolt-Glaser & Glaser, 2002). Consequently, MDD is also associated with increased risk of MetS: among individuals with MDD, the prevalence of MetS is 30.5%, a rate 1.5 times higher than the control participants without MDD (Vancampfort et al., 2014). Disease risk is increased even in individuals with subclinical depressive symptoms (Kiecolt-Glaser & Glaser, 2002). The relationship between MDD and MetS appears to be bidirectional, as MetS is also associated with increased risk of developing MDD (Pan et al., 2012; Vancampfort et al., 2014). MDD has also been shown to increase risk of cardiometabolic diseases associated with MetS, including a 50% increase in risk of developing CVD (Niranjan et al., 2012), and a 60% increase in risk of T2D (Mezuk et al., 2008). Comorbid MDD is seen in one out of every five CVD patients (Elderon & Whooley, 2013; Thombs et al., 2006), and in 18% to 28% of male and female patients with T2D, respectively (R. J. Anderson et al., 2001).

Depression and Inflammation

Several factors contribute to the observed relationship between MDD and MetS, with underlying inflammatory responses representing a plausible driving mechanism (Pan et al., 2012). While not all cases of MDD are associated with heightened inflammation, increased inflammation is common in MDD patients. For example, a meta-analysis including more than 10,000 individuals found that MDD patients on average had higher levels of pro-inflammatory cytokines compared to non-depressed control participants, including CRP, IL-6, IL-12, Il-18, and TNF-α, alongside lower levels of the anti-inflammatory cytokine IL-4 (Osimo et al., 2020). Past research has also found that medical treatment with pro-inflammatory cytokines, such as IFN treatment for hepatitis, including IFN-β, IFN-γ, and in particular IFN-α, has the ability to induce depressive symptoms and MDD, suggesting that inflammation can be a causal factor (Horikawa et al., 2003; Kraus et al., 2005; Loftis & Hauser, 2004; Lotrich, 2015).

Administration of LPS has been shown to increase both circulating pro-inflammatory cytokines (IL-6 and TNF-α) and depressive symptoms, even in healthy individuals (DellaGioia &

Hannestad, 2010; Irwin et al., 2019). Because administration of LPS and associated inflammation can induce depressive symptoms, and absorption of LPS across the intestinal barrier is an important mechanism in the development of diet-induced inflammation (Cani, 2018; Cani et al., 2007), it is plausible that the pro-inflammatory effects of poor diet quality could contribute to the development of depression. Additionally, research has found a significant association between the magnitude of *ex vivo* LPS-stimulated inflammatory responses and current/remitted clinical MDD; however, only IL-8 production remained significant after adjusting for lifestyle variables (Vogelzangs et al., 2016). Other studies have also found significant associations between *ex vivo* LPS stimulated inflammatory responses and symptoms of MDD, primarily symptoms associated with sickness behavior (van Eeden et al., 2020), with evidence for sex differences in the relationship (Knight et al., 2020; Majd et al., 2018).

Depression and Diet Quality

Individuals with MDD tend to consume a lower-quality diet compared to non-depressed individuals (Berk & Jacka, 2019; Quirk et al., 2013). The direction of the association remains unclear (Jacka et al., 2015), and randomized controlled trials examining this association in humans are rare (Jacka & Berk, 2013). However, mounting epidemiological evidence suggests that poor diet quality independently increases depression risk, likely via nutrient-microbiome interactions and associated inflammation (Berk et al., 2013; Dash et al., 2015; Jacka & Berk, 2013). Substantial evidence suggests that individual nutrients have pro- or anti-inflammatory properties (Nabavi et al., 2017; Nobs et al., 2020), but less is known about how overall diet quality impacts inflammation. Similarly, specific nutrients have been associated with MDD risk, including B vitamins (Almeida et al., 2015; Moore et al., 2019; Skarupski et al., 2010), vitamin D (Parker et al., 2017; Spedding, 2014), and omega-3 PUFA (Jazayeri et al., 2008; Logan, 2004; Su et al., 2003), with evidence suggesting that nutrient supplementation can reduce depressive symptoms (Almeida et al., 2015; Moore et al., 2019; Spedding, 2014; Su et al., 2003).

In 2006, Sanchez-Villegas and colleagues published findings that adherence to the Mediterranean diet pattern, well-known for its cardioprotective and anti-inflammatory properties (Giugliano & Esposito, 2008; Panagiotakos et al., 2006), is associated with reduced risk of developing MDD within 10 years (Sánchez-Villegas et al., 2006). Later, Akbaraly and colleagues found that consumption of a dietary pattern high in processed foods (e.g., processed meat, desserts, fried food, and refined grains) was associated with a 58% increase in odds of developing depression across a five year period compared to dietary patterns high in whole foods (e.g., fruit, vegetables, and fish) (Akbaraly et al., 2009). Other studies have also reported that diet quality predicts risk of MDD in adolescents (Jacka et al., 2011; Oddy et al., 2009; Weng et al., 2012), middle-aged adults (Jacka et al., 2010; Jacka, Mykletun, et al., 2011; Lai et al., 2017; Nanri et al., 2010), and older adults (Samieri et al., 2008). One study reported significant inverse associations between HEI-2005 diet quality scores and depression risk (Kuczmarski et al., 2010). It has been posited that diet influences MDD risk via nutrient-microbiome interactions and associated inflammation (Carlessi et al., 2021; Dash et al., 2015; Evrensel & Ceylan, 2015). This gut-immune axis influences immune system function in a manner that can promote inflammation within the central nervous system, an important process in the development of inflammation-related MDD (Carlessi et al., 2021; Dash et al., 2015). However, additional research is needed to elucidate the degree of MDD risk associated with varying levels of diet quality.

College Students

The transition to college is a period of dramatic change, and as such is stressful (Conley et al., 2014, 2020). Most students move out of their parental home to enter the first semester of college, an important step in the journey to independence (Bowman et al., 2019; Butler et al., 2004). This relocation results in exposure to a new social and physical environment, requiring cognitive and behavioral adaptations with implications for physical and mental health (Bowman et al., 2019; Butler et al., 2004). For example, across the first year of college, diet quality tends

to decline (Butler et al., 2004; Small et al., 2013) while body weight and body fat percentage increase (Beaudry et al., 2019; Racette et al., 2005; Vadeboncoeur et al., 2015; Wengreen & Moncur, 2009). A meta-analysis including 5549 students found that 60.9% gained a significant amount of weight in the first year; students gained 7.5lbs on average, a rate five times higher than the overall US adult population (Vadeboncoeur et al., 2015). Indeed, significant increases in body weight are seen within the first semester of entering college (Ludy et al., 2018). Past research has shown that students with the largest decline in diet quality across the first year of college also tend to gain the most weight (Pliner & Saunders, 2008). Given that chronic stress (Cohen et al., 2012), poor diet quality (Nobs et al., 2020) and abdominal obesity (Elks & Francis, 2010) are all associated with the development of chronic inflammation, and chronic inflammation contributes to the development of MetS (Scarpellini & Tack, 2012), these adverse changes may confer substantial increases in long-term disease risk. As such, the first semester of college may be an ideal time to implement programs and policies aimed at improving diet quality to reduce disease risk. However, to optimize future intervention strategies, further research is needed to better identify at-risk college students, and to identify the level of diet quality associated with risk factor development in this vulnerable population.

Diet Quality and the Transition to College

Past research has consistently found that diet quality tends to decline across the first year of college (Butler et al., 2004; Pliner & Saunders, 2008; Wengreen & Moncur, 2009). Intriguingly, total calories consumed per day tend to remain similar (Hajhosseini et al., 2006) or even decline across the first year of college (Butler et al., 2004), despite weight being gained. Instead of increasing calorie consumption, declining diet quality may contribute to the observed weight gain in the first year of college, particularly for students residing on campus (Yoon et al., 2014). Two broad factors seem to drive the decrease in diet quality across the first year of college: decreasing fruit and vegetable consumption, and increasing sweet snacks/desserts, savory snacks, high fat meats, and soft drinks (Pliner & Saunders, 2008). However, only

decreasing fruit and vegetable consumption independently predicted change in BMI (Pliner & Saunders, 2008), suggesting that this aspect of diet quality may be of particular importance.

Evidence suggests that students residing on-campus have similar BMIs compared to off-campus students, despite having higher physical activity levels (i.e., taking 30% more steps per day); this apparent contradiction was explained by the significantly worse diet quality in on-campus residents (Yoon et al., 2014). However, these associations were only significant in female students, for whom on-campus living was associated with lower intake of vitamins C and E, higher intake of monounsaturated fatty acids (MUFA), higher intake of total calories, and higher intake of alcohol, compared to off-campus counterparts. The lack of significant differences in males may have been due to the small number of male participants, of whom only 9 resided on campus. Highlighting this, while female on-campus residents consumed 283 calories/day more than off-campus females, on-campus male students consumed 370 more calories/day than off-campus male students (Yoon et al., 2014).

Intriguingly, MUFA consumption, despite generally being seen as neutral to beneficial for health (Gillingham et al., 2011; Kris-Etherton, 1999; Mazidi et al., 2020), may contribute to the development of endotoxemia, as oleic acid (a type of MUFA) has been found to increase intestinal permeability and upregulate LPS absorption across the intestinal barrier in several animal models (Kelly et al., 2012). Consumption of alcohol has similarly been shown to increase intestinal permeability and the absorption of LPS (Purohit et al., 2008). Conversely, vitamins C (Abhilash et al., 2014) and E (Lewis et al., 2019) have been shown to have anti-inflammatory properties, including suppression of the NF-κB pathway. On-campus residing students, such as most first-year students at Penn State, may therefore be at particularly high risk of developing chronic inflammation and/or MetS due to their specific dietary patterns. While alcohol use is also associated with weight gain in first-year students, this relationship may be a function not only of the caloric content of alcoholic beverages, but also of changes in diet quality surrounding drinking episodes (Lloyd-Richardson et al., 2008). Eating habits after drinking, such as frequent

consumption of high-fat foods in large portion sizes, predict change in BMI both in the first semester of college and across the first year (Lloyd-Richardson et al., 2008).

Given that both weight gain (Suzuki & Akamatsu, 2014) and low consumption of fruits and vegetables (Kim, 2019; Tian et al., 2018) contribute to MetS development, the weight gain and poor dietary habits developed in the first year of college could substantially increase MetS risk in students, and therefore increase long term disease risk (Rao et al., 2014). Of particular interest here, fruits and vegetables have been shown to have anti-inflammatory effects (Hosseini et al., 2018), while alcohol (Waldschmidt et al., 2008), saturated fats (Enos et al., 2013), and sugars (Della Corte et al., 2018) have pro-inflammatory effects. Thus, it is plausible that the changes in diet quality that occur during the transition into college could increase risk of obesity and MetS by promoting inflammation.

Depression and the Transition to College

Alongside these adverse changes in diet quality and body composition, mental health also tends to decline across the first year of college. One in three college students experience clinically significant mental health issues (Auerbach et al., 2018), and rates of mental health problems within the college student population have been increasing across time (Xiao et al., 2017). Depression is the most commonly experienced psychological disorder in college students, with a systematic review of 24 studies reporting that approximately 30.6% of college students meet diagnostic criteria for MDD (Ibrahim et al., 2013). For comparison, the Centers for Disease Control and Prevention most recently estimated the prevalence of MDD in the general US adult population to be 8.1% (Brody et al., 2018). Studies reporting changes in depression across the first semester are rare, and somewhat inconsistent. One study found that 38.8% of first-year students had clinically significant depressive symptoms at baseline, increasing significantly to 50.3% of students by the end of the first semester (Barker et al., 2018). Similarly, a second study reported that 49% of first year veterinary students suffered from depression at baseline, increasing to 65% by the end of the first semester (Reisbig et al., 2012). A third study

reported no significant change in depressive symptoms across the first semester but noted substantial heterogeneity, with change scores ranging from -19 to +21; social support was found to be the strongest predictor of change in depression in this sample (Arigo & Cavanaugh, 2016). The ongoing Coronavirus disease 2019 (COVID-19) pandemic appears to exacerbating mental health problems, with one high-quality publication finding a 3-fold increase in depression rates during the pandemic compared to pre-pandemic levels (Ettman et al., 2020).

Development of depression is complex and multi-faceted (for an in-depth discussion of depression, please see Chapter 2.4), but research suggests that academic and general life stress are among the strongest predictors of depression in college students (Lester, 2014). This is particularly true for first-year students, most of whom report increased stress compared to high school levels (Rayle & Chung, 2007). Transitioning from high school to college is also associated with increased depression, most of which develops across the first semester (Kroshus et al., 2021). Between the summer and the end of the fall semester, first-year students experienced a 25% increase in depressive symptoms (Kroshus et al., 2021). Additional increases across the spring semester were not significant, highlighting the importance of the first semester for mental health outcomes (Kroshus et al., 2021). In the same study, chronic stress was found to be the strongest predictor of depressive symptoms (Kroshus et al., 2021). Because chronic stress is associated with chronic inflammation (Cohen et al., 2012; G. E. Miller et al., 2002), and chronic inflammation can promote the development of depression (Kiecolt-Glaser et al., 2015), it is plausible that the association between chronic stress and depressive symptoms in college students is mediated by inflammatory mechanisms.

Past research has also found that depression is associated with declining diet quality in the college student population (Keck et al., 2020; Wattick et al., 2018). Upon examination of dietary components, high intake of sugar was associated increased risk of depression for both female and male students, while low fruit and vegetable consumption predicted depression in males only (Keck et al., 2020; Wattick et al., 2018). Keck and colleagues (2020) also found a

significant association between dietary saturated fat intake and depression risk, which was not observed by Wattick and colleagues (2018).

Hypotheses

Based on the evidence described above, we hypothesized that:

1. Poorer diet quality would be associated with concurrently a) heightened depressive symptoms and b) worse MetS symptom severity at both visits.
2. Poorer diet quality would be associated with concurrently a) higher levels of circulating cytokines, and b) heightened production of cytokines in response to *ex vivo* stimulation with LPS at both visits.
3. Higher levels of circulating cytokines would be associated with concurrently a) heightened depressive symptoms and b) worse MetS symptom severity at both study visits; higher stimulated cytokine production would also be associated with concurrently c) heightened depressive symptoms and d) worse MetS symptom severity at both study visits.
4. From visit 1 to visit 2 (i.e., across the first semester of college): a) diet quality would decline, while b) circulating cytokines, c) *ex vivo* stimulated cytokine production, d) depressive symptoms, and e) MetS symptom severity would increase.
5. Larger decreases in diet quality between visit 1 and visit 2 would be associated with a) higher levels of circulating cytokines, b) higher levels of *ex vivo* stimulated cytokine production, c) heightened depressive symptoms, and d) worse MetS symptom severity at visit 2.

Chapter 3: Methods

Overview

This study used a repeated measures design with two measurement occasions, one each at the beginning and the end of the fall 2021 semester. The study occurred in 3 parts: 1) screening, 2) visit 1 measures, and 3) visit 2 measures. Due to the ongoing COVID-19 pandemic, all questionnaire-type data were collected remotely online, while biological and anthropometric measures were collected via in-lab appointments.

Participants

Inclusion Criteria

Incoming first-year students at the Pennsylvania State University, who had graduated from high school in the spring of 2021 and were between the ages of 18-22 years, of any sex/gender and any race/ethnicity were potentially eligible for participation.

Exclusion Criteria

Potential participants were excluded if they were 1) pregnant or breastfeeding, 2) taking prescription anti-inflammatory drugs as part of a daily regimen, or 3) weighed <110 pounds at visit 1. Participants were also excluded if they had enrolled in college classes during the summer of 2021.

Procedures

Recruitment

Subjects were recruited from the Penn State, University Park campus in Centre County, PA. Advertisements via social media, flyers, emails, and class announcements were used to recruit participants. Flyers were distributed around campus and the downtown State College area. All advertisements included a description of the study, inclusion criteria, and contact information.

Screening and Informed Consent

All screening procedures were conducted remotely (via telephone or email) to minimize in-person contact. The screening and informed consent procedures were as follows:

1) The study procedure was explained to the potential participant in detail.

2) Eligibility based on inclusion and exclusion criteria was determined.

3) Eligible subjects were invited to participate in the study; a Zoom meeting was scheduled for conducting informed consent procedures.

4) Informed consent was obtained via virtual meeting prior to initiating any measurement procedures. Participants were asked to e-sign the consent form.

5) An in-lab visit was scheduled.

In-Lab Visits

Visit 1 appointments took place within the first month of the start of the participants' first semester in college, and lasted approximately 30-35 minutes. Visits were held at Penn State's Clinical Research Center (CRC), an on-campus facility for use in human subjects research. The second in-lab visit occurred approximately 4 months later, during the final 2 weeks of classes after Thanksgiving Break and before the start of finals week; this appointment repeated the measures completed at visit 1, and lasted approximately 25-30 minutes.

Participants were asked to fast for ≥ 8 hours prior to their laboratory visits in order to reduce variability from postprandial changes in circulating lipids and inflammatory cytokines (Alipour et al., 2007; Klop et al., 2012). Participants were also asked to avoid caffeine (James, 2004; Paiva et al., 2019) and strenuous exercise (Metsios et al., 2020; Ostrowski et al., 1999) on the morning of each visit to reduce variability in inflammatory cytokines and blood pressure. To reduce variability caused by diurnal fluctuations (Petrovsky et al., 1998; Zhou et al., 2010), all appointments were scheduled to begin between 8:00am and 11:00am. Because acute illness can alter inflammatory cytokine levels (Watkins et al., 1995), participants were asked if they were experiencing illness symptoms prior to beginning data collection, and appointments were rescheduled as needed.

The in-person appointment included the following components:

1. A trained research assistant met the participant outside the lab space and screened the participant for COVID-19. The Institutional Review Board (IRB) required a COVID-19 screening for all in-person study visits due to the ongoing public health concern. As required by the IRB, this screening included a short questionnaire regarding symptoms and possible exposures, as well as a temperature check using a no-touch thermometer. This temperature check was used to screen for participants with a fever (≥ 100.4^{OF}), which would indicate a potential illness or infection with COVID-19. Participants with a fever were asked to reschedule their appointments (*2 minutes).*
2. The CRC intake form was completed by the participant (*5 minutes; visit 1 only).*
3. Height & weight were measured by a trained research assistant or CRC nurse (*2 minutes; both visits).*
4. Waist circumference was measured by 2 trained research assistants or CRC nurses (*3 minutes; both visits).*
5. Blood pressure was measured by a CRC nurse or trained research assistant (*10 minutes; both visits).*
6. A blood sample was drawn by a CRC nurse. Blood was collected in ethylenediaminetetraacetic acid (EDTA) tubes to assess inflammatory markers and fasting glucose; blood was also collected in a serum separator tubes to assess blood lipids (*10 minutes; both visits).*

In-Lab Measures

Height and Weight

Height and weight were measured by a trained research assistant or CRC nurse using a scale with an attached stadiometer. Participants were asked to remove their shoes, outerwear, and any items in pockets before stepping on to the scale. Both height and weight were measured twice, asking the participant to step off the scale and back on again between the

measurements. Height was measured to the nearest 0.1 cm; if the first two measures differed by > 0.5 cm, a third measure was taken. Similarly, if the two weight measures differed by more than 0.5 kg, a third measure of weight was taken. The average of the two most similar measures was used.

Waist Circumference

Two research staff members were present for waist circumference measurement. To achieve more consistent measurements, a tape measure with a tension-indicating compression spring was used. Participants were asked to stand comfortably with their spine upright, relax their abdominal area, and breathe normally. Waist circumference was measured in the horizontal plane at 1 cm above the navel, with the tape measure against bare skin. Participants were not asked to remove any clothing, but were asked to lift their shirt to at least 1 cm above the navel. Research staff measured 1 cm above the navel using a measuring tape, and marked the location with washable marker or tape. Staff members stood on opposite sides of the participant, and wrapped the tape measure around the participant's waist horizontally at the level of the 1 cm above the navel mark. Emphasis was placed on ensuring that the tape measure was horizontal across the entire waist circumference; inclusion of a second staff member was intended to facilitate accurate measurement. Waist circumference was measured twice, to the nearest 0.1 cm; if the first two measures differed by > 0.5 cm, a third measurement was taken. The average of the two most similar measures was used.

Blood Pressure

Blood pressure was measured by a CRC nurse using the left arm if possible; if the right arm had to be used for medical reasons, this was noted on the data collection form. Prior to initiating blood pressure measures, participants were fitted with an appropriately sized blood pressure cuff, and asked to rest quietly in a seated position for 5 minutes. After the 5-minute rest period, study staff asked the participant to remain seated with legs uncrossed and both feet flat on the floor for the duration of the blood pressure measures. Blood pressure was measured

three times, with a 1-minute break in between the readings. The average of the three blood pressure readings was used.

Blood Sample

Venous blood samples were taken by nurses at the CRC. A portion of the blood was collected in two EDTA tubes, which are recommended for use in measuring inflammatory cytokines (Flower et al., 2000); one serum tube was also collected for use in measuring blood lipids. Samples were processed according to standard laboratory protocols. For analysis of circulating cytokines and fasting glucose, one EDTA tube was centrifuged immediately after collection (15 minutes at 2200 RPM). The second EDTA tube was collected for use in the stimulated cytokine assay (see the next section for details). Serum tubes were allowed to clot for 30 minutes at room temperature before centrifuging (15 minutes at 2200 RPM). After centrifugation, the supernatant was aliquoted into 2 mL cryovials and stored in a locked -80 ºC freezer in the Biomarker Core Laboratory in the Health and Human Development building on campus until being batch processed at the end of the study period. The Biomarker Core Laboratory conducted assays for circulating cytokines using commercially available multiplex assay kits (MesoScale Discovery, 2018); fasting blood glucose, triglycerides, and HDL-C were assayed using a Roche Diagnostic Cobas c311 chemistry analyzer (Roche Diagnostics, Basel, Switzerland).

Stimulated Cytokines

To measure stimulated cytokine production, samples were assayed using the exact protocol described in the MesoScale Diagnostics User Manual (MesoScale Discovery, 2018); this assay was conducted in collaboration with the Stress and Immunity Lab at Penn State. Briefly, 3 mL of LPS solution (derived from *E. coli* serotype 055:B5, no. L-2880; Sigma-Aldrich Co., St. Louis, MO) was added to 1 mL whole blood samples (collected in an EDTA tube) to form a 1 µg/mL LPS solution. Tubes, with their caps removed, were then placed in an incubator on a rotational shaker (maintained at 37 ºC and 5% CO_2) and incubated for 4 hours. After

incubation, samples were centrifuged (1500 x g for 15 minutes), and then aliquoted into 2 mL cryovials. Samples were then stored at −80 °C until being batch processed at the end of the study period; all samples from the same participant were assayed on the same plate to reduce variability. Median lower limits of detection are 0.06 pg/mL for IL-6, 0.05 pg/mL for IL-1β, and 0.37 pg/mL for IFN-γ (MesoScale Discovery, 2018).

Online Measures

Due to the ongoing COVID-19 pandemic, efforts were made to ensure minimal in-person measures and thus reduce social contact. Thus, all psychometric and dietary questionnaires were collected remotely online. Diet recalls were collected online using the Automated Self-Administered 24-Hour (ASA24) diet recall system, which provides unique, de-identified login information to each participant. All other questionnaires were entered into Penn State's Research Electronic Data Capture (REDCap); participants were able to log in to REDCap using their study identification number to protect privacy. For a summary of self-report scales, please see Table 3. To see the full questionnaires used, please refer to the Appendix.

Table 3: Summary of Self-Report Scales

Construct	Measure	Subscales	Administration Time	Measurement Time Point
Diet quality	ASA24 (collection method) HEI-2015 (scoring method)	Total Fruits Whole fruits Total vegetables Greens and beans Whole grains Dairy Total protein foods Seafood and plant proteins Fatty Acids Refined grains Sodium Added Sugars Saturated Fats	30 minutes per diet recall 3 diet recalls per time point 3 hours total	Visit 1; Visit 2
Depression	BDI-II	N/A	<10 minutes per time point <20 minutes total	Visit 1; Visit 2

Note. ASA24, Automated Self-Administered 24-Hour Dietary Assessment Tool; HEI-2015, Healthy Eating Index – 2015; BDI-II, Beck Depression Inventory, 2nd edition

Diet Assessment

Diet recalls were completed by the participants outside of the laboratory space. The ASA24 Dietary Assessment Tool was used to administer the 24-hour diet recall measures, in accordance with ASA24 instructions (Epidemiology & Genomics Research Program et al., 2020). In this online system, participants provide information about all foods, beverages, and supplements consumed in the 24 hours prior to completing the diet recall questionnaire. To yield a more accurate assessment of diet quality, participants were asked to complete the ASA24 three times each at visit 1 and visit 2, within two weeks of their in-lab appointment. Participants were asked to complete the recalls on three consecutive days: Thursday, Friday, and Saturday. Each participant was provided unique login information for the ASA24 system, and was sent a link via email for each diet recall. Time spent on the diet recall may vary depending on the diet of the participant, but was estimated to take approximately 30 minutes per assessment.

To protect confidentiality, unique participant identification numbers were used for the 24-hour recalls; no personal identifying information about any participants was entered into the ASA24 system. The ASA24 system uses the meal information entered by participants to generate detailed data about dietary composition, including information about food groups and specific nutrients. Diet quality was calculated using the Healthy Eating Index-2015 (HEI-2015) (Krebs-Smith et al., 2018). Code that can be used to calculate HEI-2015 scores from ASA24 data is publicly available through the National Institutes of Health (https://epi.grants.cancer.gov/hei/sas-code.html), and was used to calculate continuous HEI-2015 scores as an indicator of diet quality. Additionally, ASA24 calculates scores for each of the 13 HEI-2015 components as part of its publicly available code. Scores for each component of diet quality were also calculated for potential exploratory analyses regarding the impact of specific dietary components on measures of physical and psychological health.

Depressive Symptoms

The Beck Depression Inventory, 2nd edition (BDI-II, Beck et al., 1996), was used to assess depressive symptoms; this widely-used psychometric tool has been validated in college student samples (α's = 0.74 - 0.9) (Storch et al., 2004; Whisman et al., 2000). The BDI-II is a 21-item inventory in which participants indicate the degree to which they have experienced each of the items within the past 2 weeks on a Likert scale. While past research suggests that the BDI-II may represent two factors of depression in college students (cognitive-affective and somatic symptoms), these factors were highly correlated *(*r = .77, p < .001) (Storch et al., 2004). Consequently, depressive symptoms were treated as a single construct in the present study. In addition, given the focus on depressive symptom severity, the BDI-II score was used as a continuous variable.

Covariates

Lifestyle factors were assessed using questionnaires at both visit 1 and visit 2 for use as covariates. Participants were asked to report level of physical activity using the Godin-Shephard Leisure Time Physical Activity Questionnaire (Godin, 2011). This questionnaire describes three levels of physical activity (light, moderate, and strenuous), and asks participants to report how many times in the past week they have engaged in each level of activity for at least 15 minutes, providing a simple assessment of general physical activity; the health relevant physical activity score described by Godin (2011) was used. The Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989) was used to assess sleep quality over the last month. Finally, the Perceived Stress Scale (PSS) was used to evaluate student stress levels (Cohen et al., 1983); the PSS is a widely used measure of stress that is well-validated in college student samples (E. H. Lee, 2012). The PSS is a 10-item inventory; participants are asked to what degree they have experienced each of the 10 items within the past month on a 0 (never) to 4 (very often) Likert scale.

Missing Data and Drop Outs

Given the repeated measures design, it was expected that some participants would drop out prior to completing the full study protocol. All observations were included in the proposed analyses, and were deemed valid under the missing-at-random assumptions (Schafer & Graham, 2002). When > 5% but < 40% of data were missing for a given variable, multiple imputation was used to generate missing values (Jakobsen et al., 2017). The R packages VIM (Kowarik & Templ, 2016) and mice (van Buuren & Groothuis-Oudshoorn, 2011) were used to asses missingness and impute data. Five iterations were generated, and the final pooled data set was used in statistical analyses. When < 5% of cases were missing for a given variable, complete cases analysis was used.

Analyses

Overview

Analyses were conducted in R (R Core Team, 2014) and SAS (SAS Institute, Cary, NC). Variables were assessed for normality using Q-Q plots (Pleil, 2016); non-normally distributed variables were transformed as needed. Assessment of missingness revealed that several variables were missing between 5% and 40% of observations: BMI at visit 2 (missing 7 cases), HEI-2015 score at visit 2 (9 missing), BDI-II score at visit 1 (10 missing) and visit 2 (11 missing), MetS symptom severity at visit 2 (9 missing), sleep quality at visit 1 (8 missing) and visit 2 (16 missing), physical activity at visit 2 (10 missing), and perceived stress at visit 2 (11 missing). Visit 2 had a greater number of missing values because 7 participants did not return for a second visit: of these, 5 were not invited to return due to failure to comply with study protocols at visit 1, and 2 were lost to follow up. The 7 participants who did not return for visit 2 constituted approximately 6.4% of the overall sample; consequently, all variables were missing > 5% of observations at visit 2. For the questionnaire data, participants were informed that they were not obligated to answer all of the items, and that they could skip any questions that they were not comfortable answering. If a participant did not respond to all of the items in a scale, then an overall score for that scale could not be accurately computed; much of the missing

questionnaire data at both study visits resulted from participants not answering all questions on a particular scale.

Individuals with CRP > 10 mg/L had all inflammatory marker data for that visit removed from the analyses; at visit 1, 9 participants had CRP >10 mg/L, and at visit 2, 13 participants had CRP >10 mg/L. Data for these participants were not imputed, resulting in 9 and 13 participants having missing cytokine data at visits 1 and 2, respectively. After inflammatory data from these participants were removed, outliers greater than three standard deviations above the mean for each cytokine were removed. Then, missingness was assessed.

Not including the participants with CRP >10, no cytokine, circulating or stimulated, had greater than 5% of cases missing at visit 1. Among circulating cytokines at visit 1, IFN-γ was missing 4 observations, IL-6 was missing 2 observations, and IL-1β was missing 1 observation. Among stimulated cytokines at visit 1, IFN-y was missing 1 observation; no data were missing for stimulated IL-6 or IL-1B. All of the missing circulating and stimulated cytokine data at visit 1 that was imputed resulted from removal of outliers. At visit 2, all cytokines had > 5% missing cases, primarily because of the 7 participants who did not return for this visit. Among circulating cytokines at visit 2, IFN-γ was missing 12 observations, IL-6 was missing 10 observations, and IL-1β was missing 11 observations. In addition to the 7 participants who dropped out of the study, an insufficient blood sample was obtained from 1 participant at visit 2, and no cytokine data could be obtained. The remaining missing data (4 for IFN-y, 2 for IL-6, and 3 for IL-1B) resulted from the removal of outliers. All three stimulated cytokines were missing exactly 8 observations at visit 2, due to the 7 participants who dropped out and the 1 participant from whom an inadequate blood sample was obtained. For any cytokine missing > 5% of cases, data were imputed. However, data for the participants with CRP >10, indicating a potential infection, were not imputed.

As a preliminary analysis, t-tests were used to test for mean differences in relevant covariates, individual pro-inflammatory cytokines, and other variables of interest between visit 1

and visit 2 measures (see Supplementary Table 1). For all analyses, significance was accepted at $p<0.05$.

Metabolic Syndrome Symptom Severity Score

It was expected that only a small percentage of students would meet full diagnostic criteria for MetS (Dalleck & Kjelland, 2012; Higgins et al., 2020). However, past research has produced equations for calculating sex- and race- specific MetS symptom severity scores based on ATP-III criteria that can be used in younger samples (Gurka et al., 2012). In an effort to make this MetS symptom severity equation more clinically useful, BMI is substituted for waist circumference (Gurka et al., 2012). Because BMI is included as a component of the MetS symptom severity score, and equations are sex-specific, regression models with MetS symptom severity as the outcome did not include BMI and sex as covariates. Sleep quality, perceived stress, and physical activity were included as relevant covariates in these regression models. Specific equations are provided for Non-Hispanic White, Non-Hispanic Black, and Hispanic samples; however, no equation is provided for people of Asian descent. The present study included 13 participants who identified as Asian. We contacted the study authors, asking for clarification about whether any equations were suitable for use with Asian participants. The study group advised including Asian individuals with Non-Hispanic White individuals, as there is not yet sufficient evidence to indicate that MetS manifests differently in Asian individuals (M. DeBoer, personal communication, June 9, 2022). Consequently, the equation for Non-Hispanic White participants was applied to Asian participants as well. Sensitivity analyses were conducted to determine whether including Asian participants in this category impacted study results relative to excluding Asian participants; see Supplementary Tables 1 through 6 for details. Please see Gurka and colleagues (2012) for the specific equations used to calculate continuous MetS symptom severity scores.

Inflammatory Composite Scores

Compared to using individual cytokines, use of a composite score of inflammation reduces the number of comparisons and the type I error rate (Fagundes et al., 2019; Knight et al., 2020), and is therefore preferable. Based on existing literature, the proposed study included the inflammatory cytokines IL-6, IL-1β, and IFN-γ in the composite measures of both circulating and stimulated inflammation. Past research by this lab group has used the same composite inflammation score (Davis et al., 2020). In addition, each of these cytokines has been implicated in the development of both MetS and MDD. Past research has also found IL-6 (Kanda & Takahashi, 2004), IL-1β (Ballak et al., 2015), and IFN-γ (Arababadi et al., 2009; Schroecksnadel et al., 2006) to be primary contributors to CVD and T2D development. In addition, IL-6 (Howren et al., 2009), IL-1β (Howren et al., 2009), and IFN-γ (Berk et al., 2013) have all been implicated in the pathology of MDD. Thus, the literature provides empirical support for the use of this inflammatory composite score.

Prior to calculating the composite scores, inflammatory data for individuals with CRP >10 mg/L, a clinical cutoff that may indicate current infection, were removed (Jonker et al., 2017; Niles et al., 2018). Under conditions of infection, inflammatory markers are typically elevated, and immune system function is altered (Anand & Kanneganti, 2013; C. Shi & Pamer, 2011), making inflammation-related data from these participants potentially incomparable to the rest of the sample. To calculate the composite score for circulating cytokines at visit 1, measures of each cytokine (IL-6, IL-1β, and IFN-α) taken at visit 1 were Z-score standardized (i.e., z_IL6, z_IL1β, and z_IFNα). The standardized values for each cytokine were then summed together, resulting in a single composite score for visit 1 circulating cytokines. These steps were repeated to calculate composite scores for *ex vivo* stimulated cytokine production at visit 1. The same process was then used to calculate composite scores for circulating cytokines and *ex vivo* stimulated cytokine production at visit 2.

Statistical Analyses

Hypothesis 1a-1b: Poorer diet quality would be associated with concurrently 1a) heightened depressive symptoms, and 1b) worse MetS symptom severity at both visit 1 and visit 2.

First, Pearson correlations were used to examine unadjusted concurrent associations among diet quality, MetS symptom severity, and depressive symptoms at each visit. Then, separate multiple linear regression models were constructed to examine whether diet quality was significantly associated with depressive symptoms and MetS symptom severity, respectively, at each visit. Sleep quality, physical activity level, and perceived stress were included in all the initial models as covariates. For the initial models predicting depressive symptoms, sex and BMI were also included as covariates. Non-significant covariates were removed from the final model.

Hypothesis 2a-2b: Poorer diet quality would be associated with concurrently 2a) higher levels of circulating cytokines, and 2b) heightened cytokine production in response to *ex vivo* stimulation with LPS at both study visits.

Pearson correlations were used to examine unadjusted concurrent associations among diet quality, circulating pro-inflammatory cytokines, and stimulated cytokine production. Separate multiple linear regression models were then used to test whether diet quality was significantly associated with circulating pro-inflammatory cytokine levels and stimulated cytokine production, respectively, at each visit. Sex, BMI, sleep quality, physical activity level, and perceived stress were included in the initial model as covariates. Non-significant covariates were removed from the final model.

Hypotheses 3a-3d: Higher levels of circulating cytokines would be associated with concurrently 3a) heightened depressive symptoms and 3b) worse MetS symptom severity at both study visits; higher *ex vivo* stimulated cytokine production would also be associated with concurrently 3c) heightened depressive symptoms and 3d) worse MetS symptom severity at both study visits.

Pearson correlations were used to examine unadjusted concurrent associations among circulating pro-inflammatory cytokines, *ex vivo* stimulated cytokine production, depressive symptoms, and MetS symptom severity. Separate multiple linear regression analyses were used to test whether circulating cytokines were significantly associated with depressive symptoms and MetS symptom severity, respectively, at each visit. Sleep quality, physical activity level, and perceived stress were included in all the initial models as covariates. For the initial models predicting depressive symptoms, sex and BMI were also included as covariates. Non-significant covariates were removed from the final models. This process was repeated to test whether *ex vivo* stimulated cytokine production was significantly associated with depressive symptoms and MetS symptom severity at each visit.

Hypotheses 4a-4e. From visit 1 to visit 2 (i.e., across the first semester of college): 4a) diet quality would decline, while 4b) circulating cytokines, 4c) *ex vivo* stimulated cytokine production, 4d) depressive symptoms, and 4e) MetS symptom severity would increase.

Paired t-tests were used to examine whether diet quality, circulating cytokines, *ex vivo* stimulated cytokine production, depressive symptoms, and MetS symptom severity change significantly across the two visits by comparing visit 1 and visit 2 measures.

Hypotheses 5a-5d. Larger decreases in diet quality from visit 1 to visit 2 would be associated with 5a) higher levels of circulating cytokines, 5b) higher levels of cytokine production in response to *ex vivo* stimulation with LPS, 5c) heightened depressive symptoms, and 5d) worse MetS symptom severity at visit 2.

Change scores were calculated by subtracting diet quality at visit 1 from diet quality at visit 2; positive change scores therefore represent improving diet quality, while negative change scores reflect declining diet quality. Change scores for diet quality were used in multiple linear regression models to assess whether declining diet quality was associated with circulating cytokines, *ex vivo* stimulated cytokine production, depressive symptoms, and MetS symptom severity at visit 2. Sleep quality, physical activity level, and perceived stress at visit 2 were

included in all the initial models as covariates. Sex and BMI at visit 2 were also included as covariates in the initial models predicting circulating cytokines, stimulated cytokine production, and depressive symptoms; the model predicting MetS symptom severity at visit 2 did not include sex and BMI as covariates.

Chapter 4: Results

Participant characteristics

A total of 110 participants completed an in-lab appointment for visit 1; of these, five participants did not complete any diet recalls and were therefore not asked to return for a follow-up visit. Two participants were lost to attrition, and a total of 103 participants returned for visit 2 measures. Participant characteristics at visit 1 are presented in Table 4**.** At visit 1, all participants were either 18 (*n* = 100, 90.9%) or 19 (*n* = 10, 9.1%) years old. In terms of biological sex, 45 (40.9%) participants self-reported male sex, 64 (58.2%) self-reported female sex, and 1 (0.9%) did not provide information about biological sex. For gender, 44 (40.0%) of participants self-reported being men, 62 (56.4%) participants self-reported being women, and 3 (2.7%) participants self-reported being non-binary. Participants predominantly reported being heterosexual (*n* = 98, 89.1%); 8 (7.3%) reported being either bisexual or pansexual, 2 (1.8%) participants reported being gay or lesbian, 2 (1.8%) participants reported being asexual, and 1 (0.9%) was questioning. The sample largely identified as Non-Hispanic White (*n* = 78, 70.9%); 4 participants (3.6%) identified as Non-Hispanic Black, 15 (13.6%) identified as Hispanic, and 13 (11.8%) identified as Asian.

Most participants were not first-generation students (*n* = 95, 86.4%), while 12 (10.9%) were first generation students, and 1 (0.9%) preferred not to answer. The majority of participants reported living in on-campus housing (*n* = 108, 98.2%), as is required for most first-year students at Penn State; however, 1 (0.9%) participant reported living off campus, and 1 (0.9%) preferred not to answer. Most participants reported living with 1 roommate (*n* = 95, 86.4%), while 7 (6.4%) reported living with 2 roommates, and 4 (3.6%) reported living with 3 roommates. All students residing in on-campus housing must purchase a Penn State meal plan, which is reflected in our sample: 108 (98.2%) participants reported having a meal plan, while 1 (0.9%) reported not having a campus meal plan, and 1 (0.9%) did not respond to this item. Penn State offers 3 levels of meal plan per semester (1 = $2,158; 2 = $2,516; 3 = $2,809 in the fall

2021 semester). In this sample, 14 (12.7%) participants were enrolled in level 1, 79 (71.8%) in level 2, 13 (11.8%) in level 3, and 1 (0.9%) was unsure of their level. At visit 1, 18 participants (16.4%) had BDI-II scores that met the clinical diagnostic cutoff for a major depressive episode. Only 1 participant (0.9%) met full MetS diagnostic criteria at visit 1. Please see Table 5 for additional student information.

Table 4: Participant Characteristics at Visit 1

		Mean (*SD*) or *n* (%)
Age		
	18	100 (90.9%)
	19	10 (9.1%)
BMI		23.5 (3.7)
Sex		
	Male	45 (40.9%)
	Female	64 (58.2%)
	No answer	1 (0.9%)
Gender		
	Man	44 (40.0%)
	Woman	62 (56.4%)
	Non-binary	3 (2.7%)
Sexual orientation		
	Heterosexual	98 (89.1%)
	Bisexual / Pansexual	8 (7.3%)
	Gay / Lesbian	2 (1.8%)
	Asexual	2 (1.8%)
	Questioning	1 (0.9%)
Race/Ethnicity		
	NH White	78 (70.9%)
	NH Black	4 (3.6%)
	Hispanic	15 (13.6%)
	Asian	13 (11.8%)
Clinically depressed		
	Yes	18 (16.4%)
	No	92 (83.4%)
Alcoholic drinks per week		4 (5)

Note. SD, standard deviation; BMI, body mass index; NH, non-Hispanic; clinical depression defined as Beck Depression Inventory, 2nd edition (BDI-II) score ≥16

Table 5: Additional Information about Participants at Visit 1

	n (%)
First generation student	
Yes	12 (10.9%)
No	95 (86.4%)
No answer	1 (0.9%)
Live on campus	
Yes	108 (98.2%)
No	1 (0.9%)
No answer	1 (0.9%)
Number of roommates	
1	95 (86.4%)
2	7 (6.4%)
3	4 (3.6%)
Meal plan	
Yes	108 (98.2%)
No	1 (0.9%)
No answer	1 (0.9%)
Meal plan level	
1	14 (12.7%)
2	79 (71.8%)
3	13 (11.8%)
4	1 (0.9%)

Note. Fall 2021 semester meal plan levels: level 1 = $2,158 / semester; level 2 = $2,516 / semester; level 3 = $2,809 / semester

Results from Hypothesis 1

Hypothesis 1a and 1b. Poorer diet quality would be associated with concurrently 1a) heightened depressive symptoms, and 1b) worse MetS symptom severity at both visit 1 and visit 2.

At visit 1, the correlation between diet quality and BDI-II scores approached, but did not reach, statistical significance (r = -.189, p = .051), such that higher diet quality was nominally associated with lower depressive symptoms. Diet quality and MetS symptom severity were significantly and negatively correlated (r = -.419, p < .001), such that higher diet quality was significantly associated with lower MetS symptom severity. Results of these correlation analyses are presented in Table 6.

At visit 2, the correlation between diet quality and BDI-II scores was not significant r = -.073, p = .451). However, the correlation between diet quality and MetS symptom severity remained significant (r = -.355, p < .001). Results of these correlation analyses are presented in Table 7.

Table 6: Correlations between Diet Quality, Depressive Symptoms, and Metabolic Syndrome (MetS) Symptom Severity at Visit 1

	Diet quality	Depressive symptoms
Diet quality	--	
Depressive symptoms	-.189 (.051)	--
MetS symptom severity	-.419 **(.001*)**	.082 (.397)

Note. MetS, Metabolic Syndrome; values presented as *r* (*p*); *$p < .05$

Table 7: Hypothesis 1 - Correlations between Diet Quality, Depressive Symptoms, and Metabolic Syndrome (MetS) Symptom Severity at Visit 2

	Diet quality	Depressive symptoms
Diet quality	--	
Depressive symptoms	-.073 (.451)	--
MetS symptom severity	-.355 **(.001*)**	-.110 (.251)

Note. MetS, Metabolic Syndrome; values presented as *r* (*p*); *$p < .05$

In the regression analyses, diet quality was not significantly associated with depressive symptoms at either visit, though the association approached significance at visit 1 ($B = -0.104$, $p = .052$). Participant sex ($B = 1.514$, $p = .257$) and BMI ($B = -0.151$, $p = .382$) were not significantly associated with depressive symptoms at visit 1 and were removed as covariates from the subsequent model; sleep quality ($B = 1.355$, $p < .001$), physical activity ($B = -0.027$, $p = .044$), and perceived stress ($B = 0.550$, $p = .004$) at visit 1 were significant predictors and were maintained. After removing the non-significant covariates, diet quality remained non-significant (B=-0.080, $p = .110$), while sleep quality ($B = 1.307$, $p < .001$), physical activity ($B = -0.029$, $p = .035$), and perceived stress ($B = 0.619$, $p < .001$) at visit 1 remained significant predictors of depressive symptoms. At visit 2, a slightly different pattern of results emerged. Diet quality was still not a significant predictor of depressive symptoms at visit 2 ($B = -0.068$, $p = .208$). Among the covariates, BMI ($B = -0.259$, $p = .208$), physical activity ($B = -0.035$, $p = .054$) and perceived stress ($B = 0.262$, $p = .194$) at visit 2 were not significant, while sex ($B = 4.172$, $p = .006$) and sleep quality at visit 2 ($B = 1.453$, $p < .001$) were significantly associated with depressive symptoms. After removing the non-significant covariates, diet quality remained non-significant ($B = -0.060$, $p = .258$); sex ($B = 4.303$, $p = .004$) and sleep quality at visit 2 ($B = 1.481$, $p < .001$) remained significantly associated with depressive symptoms. Results of these regression analyses are presented in Table 8.

Table 8: Results of Regression Analyses Testing the Concurrent Association between Diet Quality and Depressive Symptoms at Each Visit

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 1: Test whether diet quality predicts depressive symptoms at visit 1, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 97)			
Diet quality	-0.104 (-0.053)	.052	0.399 (0.362)
Sex	1.514 (1.328)	.257	--
BMI	-0.151 (0.173)	.382	--
Sleep quality	1.355 (0.277)	**<.001***	--
Physical activity	-0.027 (0.013)	**.044***	--
Perceived stress	0.550 (0.186)	**.004***	--
Model 2: Test whether diet quality predicts depressive symptoms at visit 1, removing non-significant covariates (df = 99)			
Diet quality	-0.080 (0.049)	.110	0.387 (0.362)
Sleep quality	1.307 (0.274)	**<.001***	--
Physical activity	-0.029 (0.013)	**.035***	--
Perceived stress	0.619 (0.174)	**<.001***	--
Model 3: Test whether diet quality predicts depressive symptoms at visit 2, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 102)			
Diet quality	-0.068 (0.054)	.208	0.315 (0.2752)
Sex	4.172 (1.483)	**.006***	--
BMI	-0.259 (0.204)	.208	--
Sleep quality	1.453 (0.282)	**<.001***	--
Physical activity	-0.035 (0.018)	.054	--
Perceived stress	0.262 (0.200)	.194	--
Model 4: Test whether diet quality predicts depressive symptoms at visit 2, removing non-significant covariates (df = 105)			
Diet quality	-0.060 (0.053)	.258	0.258 (0.236)
Sex	4.303 (1.474)	**.004***	--
Sleep quality	1.481 (0.287)	**<.001***	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; BMI, body mass index; $^{*}p < .05$

At visit 1, diet quality (B = -0.024, p < .001) was the only variable included to be significantly associated with MetS symptom severity. All covariates, including: sleep quality (B = 0.017, p = .522), physical activity (B < 0.001, p = .730), and perceived stress (B = -0.005, p = .771) at visit 1 were not significantly associated with MetS symptom severity. Consequently, no subsequent model was constructed. See Figure 2 for a graphical representation of this model at visit 1. Results were similar at visit 2. Diet quality was significantly associated with MetS symptom severity (B = -0.021, p < .001). Sleep quality (B = -0.012, p = .641), physical activity (B = 0.001, p = .384), and perceived stress (B = -0.012, p = .359) at visit 2 were all not significant,

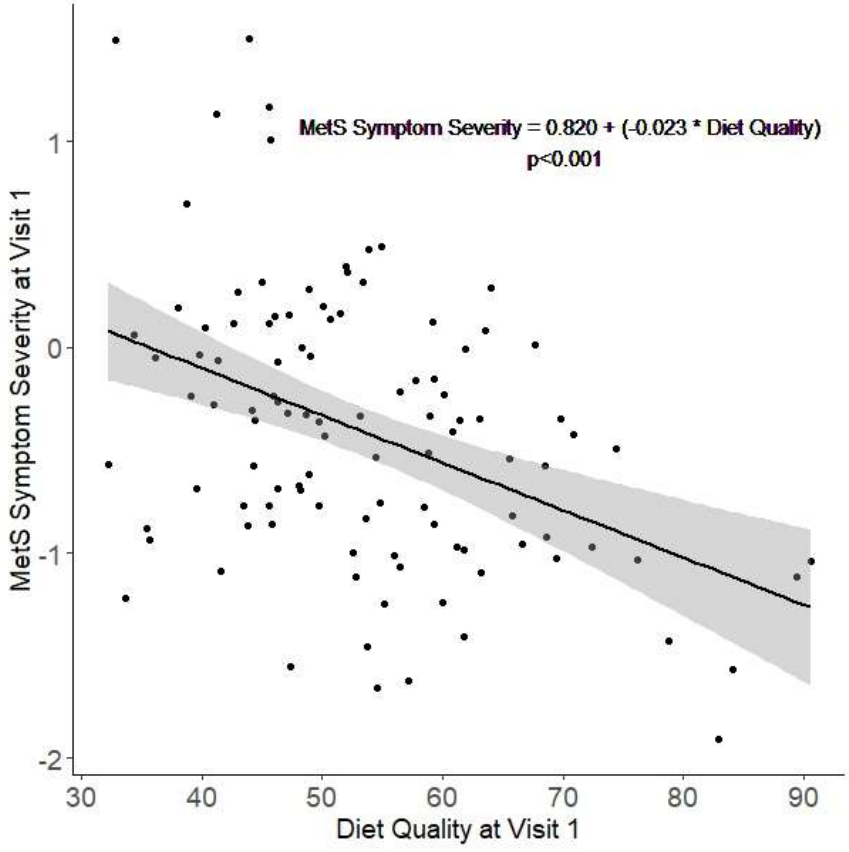
and as such no subsequent model was constructed. Results of these regression analyses are presented in Table 9. See Figure 3 for a graphical representation of this model at visit 2.

Table 9: Results of Regression Analyses Testing the Concurrent Association between Diet Quality and Metabolic Syndrome (MetS) Symptom Severity at Each Visit

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 5: Test whether diet quality predicts MetS symptom severity at visit 1, with sleep quality, physical activity, and perceived stress included as covariates (df = 99)			
Diet quality	-0.024 (0.005)	**<.001***	0.193 (0.160)
Sleep quality	0.017 (0.028)	.522	--
Physical activity	<0.001 (0.001)	.730	--
Perceived stress	-0.005 (0.017)	.771	--
Model 6: Test whether diet quality predicts MetS symptom severity at visit 2, with sleep quality, physical activity, and perceived stress included as covariates (df = 105)			
Diet quality	-0.021 (0.005)	**<.001***	0.184 (0.150)
Sleep quality	-0.012 (0.025)	.641	--
Physical activity	0.001 (0.002)	.384	--
Perceived stress	0.016 (0.017)	.359	--

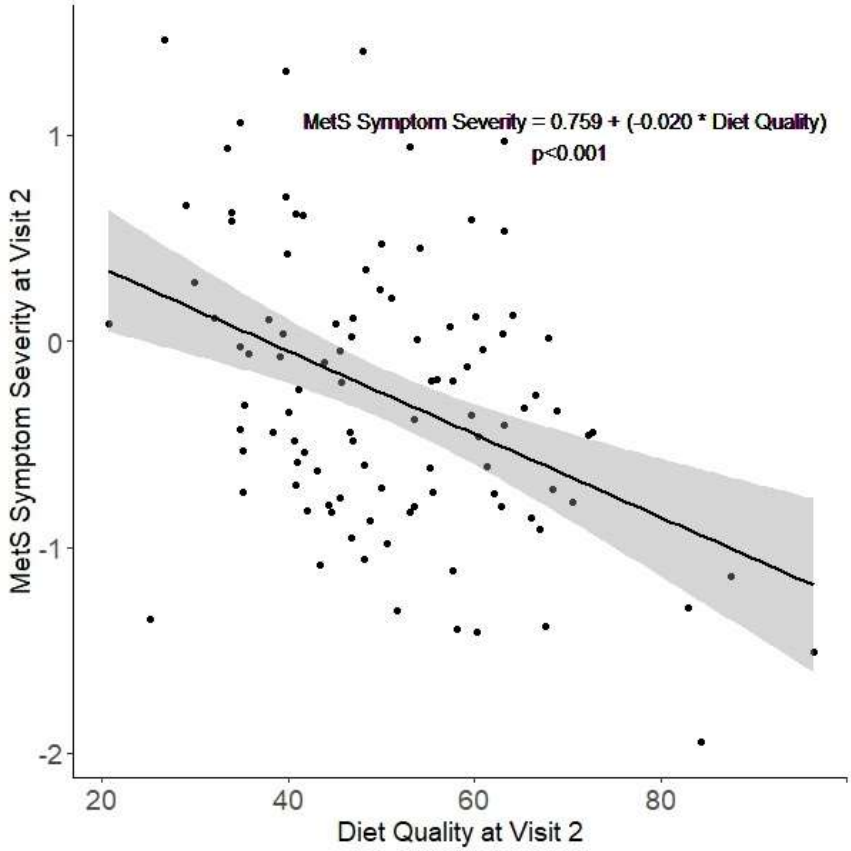
Note. SE, standard error; df, degrees of freedom; adj., adjusted; $^*p < .05$

Figure 2: Association Between Diet Quality and Metabolic Syndrome (MetS) Symptom Severity at Visit 1



Note. MetS, Metabolic Syndrome

Figure 3: Association Between Diet Quality and Metabolic Syndrome (MetS) Symptom Severity at Visit 2



Note. MetS, Metabolic Syndrome

Results from Hypothesis 2

Hypothesis 2a-2b. Poorer diet quality would be associated with concurrently 2a) higher levels of circulating cytokines, and 2b) heightened cytokine production in response to *ex vivo* stimulation with LPS at both study visits.

Diet quality was not significantly correlated with circulating cytokines or with stimulated cytokine production at visit 1 (*r*'s = -.052, -.064; *p*'s = .614, .529, respectively) or visit 2 (*r*'s = -.169, -.085; *p*'s = .100, .584, respectively). Results of these correlational analyses are presented in Table 10 and Table 11.

Table 10: Correlations between Diet Quality, Circulating Cytokines, and Stimulated Cytokines at Visit 1

	Diet quality	Circulating cytokines
Diet quality	--	
Circulating cytokines	-.052 (.614)	--
Stimulated cytokines	-.064 (.529)	.195 **(.001*)**

Note. Values presented as *r* (*p*)

Table 11: Correlations between Diet Quality, Circulating Cytokines, and Stimulated Cytokines at Visit 2

	Diet quality	Circulating cytokines
Diet quality	--	
Circulating cytokines	-.169 (.100)	--
Stimulated cytokines	-.085 (.584)	.039 **(.014*)**

Note. Values presented as *r* (*p*); $^{*}p < .05$

Similarly, in the regression analyses, no significant association was observed between diet quality and circulating pro-inflammatory cytokines at either visit. At visit 1, neither diet quality (*B* = -0.013, *p* = .596), nor any covariate, including sex (*B* = 0.096, *p* = .877), as well as concurrent BMI (*B* = 0.017, *p* = .840), sleep quality (*B* = 0.154, *p* = .236), physical activity (*B* < 0.001, *p* = .980), and perceived stress (*B* = -0.138, *p* = .127) were significantly associated with circulating pro-inflammatory cytokines. Because no covariates were significantly associated with circulating cytokines in this model, no subsequent model was constructed. Results were largely similar at visit 2. Diet quality was not associated with circulating pro-inflammatory cytokines (*B* = -0.023, *p* = .315), and most covariates also remained non-significant, including sex (*B* = -0.060, *p* = .924), BMI (*B* = 0.141, *p* = .131), physical activity (*B* = -0.005, *p* = .535), and perceived stress (*B* = -0.062, *p* = .483) at visit 2. However, sleep quality at visit 2 was significantly associated with circulating pro-inflammatory cytokines at visit 2 (*B* = -0.261, *p* = .031), indicating that poorer sleep quality was associated with concurrently higher levels of circulating pro-inflammatory cytokines. After removing the non-significant covariates, the association between diet quality and circulating pro-inflammatory cytokines remained non-significant (*B* = -0.035, *p* = .093). The association between sleep quality and circulating pro-inflammatory cytokines at viist

2 remained significant (B = -0.260, p = .027). Results of these regression analyses are presented in Table 12.

Table 12: Results of Regression Analyses Testing the Association between Diet Quality and Circulating Cytokines at Each Visit

	B (SE)	p	R^2 (adj. R^2)
Model 7: Test whether diet quality predicts circulating cytokines at visit 1, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 88)			
Diet quality	-0.013 (0.025)	.596	0.038 (-0.028)
Sex	0.096 (0.622)	.877	--
BMI	0.017 (0.084)	.840	--
Sleep quality	0.154 (0.129)	.236	--
Physical activity	<0.001 (0.006)	.980	--
Perceived stress	-0.138 (0.089)	.127	--
Model 8: Test whether diet quality predicts circulating cytokines at visit 2, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 93)			
Diet quality	-0.023 (0.022)	.315	0.111 (0.050)
Sex	-0.060 (0.620)	.924	--
BMI	0.141 (0.093)	.131	--
Sleep quality	-0.261 (0.119)	**.031***	--
Physical activity	-0.005 (0.007)	.535	--
Perceived stress	-0.062 (0.089)	.483	--
Model 9: Test whether diet quality predicts circulating cytokines at visit 2, removing non-significant covariates (df = 93)			
Diet quality	-0.035 (0.021)	.093	0.078 (0.059)
Sleep quality	-0.260 (0.116)	**.027***	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; BMI, body mass index; *p < .05

At visit 1, diet quality was not significantly associated with *ex vivo* stimulated cytokine production (B = 0.006, p = .767). Most covariates were also not significantly associated with stimulated cytokine production, including BMI (B = 0.076, p = .301), sleep quality (B = 0.005, p = .961), physical activity (B = 0.007, p = .182), and perceived stress (B = 0.011, p = .885) at visit 1. Sex, however, was significantly associated with stimulated cytokine production at visit 1 (B = -1.168, p = .033); because sex was coded as male = 1, female = 2, this association indicates that females had significantly lower cytokine production in response to *ex vivo* stimulation with LPS compared to males. After removing the non-significant covariates, the association between diet quality and stimulated cytokine production remained non-significant, (B < 0.001, p = .994), while sex remained significant (B = -1.12, p = .021). At visit 2, diet quality was not significantly

associated with stimulated cytokine production (*B* = -0.012, *p* = .541); neither were any of the covariates at the same visit: sex (*B* = -0.663, *p* = .214), BMI (*B* = -0.014, *p* = .864), sleep quality (*B* = -0.077, *p* = .450), physical activity (*B* = 0.008, *p* = .208), and perceived stress (*B* = 0.039, *p* = .605). Because no covariates were significantly associated with *ex vivo* stimulated pro-inflammatory cytokine production in this model, no subsequent model was constructed. Results of these regression analyses are presented in Table 13.

Table 13: Results of Regression Analyses Testing the Association between Diet Quality and Stimulated Cytokines at Each Visit

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 10: Test whether diet quality predicts the stimulated cytokines at visit 1, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 94)			
Diet quality	0.006 (0.022)	.767	0.056 (0.036)
Sex	-1.168 (0.540)	**.033***	--
BMI	0.076 (0.073)	.301	--
Sleep quality	0.005 (0.112)	.961	--
Physical activity	0.007 (0.005)	.182	--
Perceived stress	0.011 (0.078)	.885	--
Model 11: Test whether diet quality predicts the stimulated cytokines at visit 1, removing non-significant covariates (df = 94)			
Diet quality	<0.001 (0.020)	.994	0.056 (0.036)
Sex	-1.12 (0.479)	**.021 ***	--
Model 12: Test whether diet quality predicts the stimulated cytokines at visit 2, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 88)			
Diet quality	-0.012 (0.019)	.541	0.043 (-0.022)
Sex	-0.663 (0.530)	.214	--
BMI	-0.014 (0.079)	.864	--
Sleep quality	-0.077 (0.101)	.450	--
Physical activity	0.008 (0.006)	.208	--
Perceived stress	0.039 (0.076)	.605	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; BMI, body mass index; $^*p < .05$

Results from Hypothesis 3

Hypotheses 3a-3d. Higher levels of circulating cytokines would be associated with concurrently 3a) heightened depressive symptoms and 3b) worse MetS symptom severity at both study visits; higher *ex vivo* stimulated cytokine production would also be associated with concurrently 3c) heightened depressive symptoms and 3d) worse MetS symptom severity at both visits.

At visit 1, circulating cytokines were not associated with depressive symptoms (*r* = -.081, *p* = .419) or with MetS symptom severity (*r* = .078, *p* = .441). *Ex vivo* stimulated cytokine

production was also not associated with depressive symptoms (r = -.069, p = .496), or with MetS symptom severity at visit 1 (r = .095, p = .346). Results of these correlational analyses are presented in Table 14.

Table 14: Correlations between Inflammatory Markers, Depressive Symptoms, and Metabolic Syndrome (MetS) Symptom Severity at Visit 1

	Circulating cytokines	Stimulated cytokines	Depressive symptoms
Circulating cytokines	--		
Stimulated cytokines	.415 **(<.001*)**	--	
Depressive symptoms	-.081 (.419)	-.069 (.496)	--
MetS symptom severity	.078 (.441)	.095 (.346)	.082 (.397)

Note. MetS, Metabolic syndrome; Values presented as r (p); $^{*}p < .05$

At visit 2, circulating cytokines were not significantly associated with depressive symptoms (r = -.134, p = .193). The association between MetS symptom severity and circulating cytokines approached, but did not reach, significance (r = .204, p = .057) at visit 2. Similarly, *ex vivo* stimulated cytokine production was not associated with depressive symptoms (r = -.010, p = .921) or with MetS symptom severity (r = .069, p = .502) at visit 2. Results of these correlational analyses are presented in Table 15.

Table 15: Correlations between Inflammatory Markers, Depressive Symptoms, and Metabolic Syndrome (MetS) Symptom Severity at Visit 2

	Circulating cytokines	Stimulated cytokines	Depressive symptoms
Stimulated cytokines	.251 **(.014*)**	--	
Depressive symptoms	-.134 (.193)	-.010 (.921)	--
MetS symptom severity	.204 (.057)	.069 (.502)	-.110 (.251)

Note. MetS, Metabolic syndrome; Values presented as r (p); $^{*}p < .05$

In the regression analyses, circulating pro-inflammatory cytokines did not predict depressive symptoms (B = -0.191, p = .435) at visit 1; sex (B = 1.026, p = .468), BMI (B = -0.107, p = .569), and physical activity (B = -0.028, p = .057) at visit 1 were also not significant and were therefore removed from the subsequent model. However, sleep quality at visit 1 (B = 1.311, p < .001) and perceived stress at visit 1 (B = 0.635, p = .003) did significantly predict depressive symptoms at visit 1. After removing the non-significant covariates, the association between circulating cytokines and depressive symptoms remained non-significant (B = -0.181, p

= .460), while sleep quality (*B* = 1.211, *p* = .001) and perceived stress (*B* = 0.735, *p* < .001) at visit 1 remained significant predictors of depressive symptoms. At visit 2, circulating cytokines (*B* = -0.079, *p* = .770), BMI (*B* = -0.216, *p* = .351) and perceived stress (*B* = 0.095, *p* = .675) at visit 2 did not predict depressive symptoms, while sex (*B* = 3.884, *p* = .014), sleep quality (*B* = 1.494, *p* < .001) and physical activity (*B* = -0.045, *p* = .020) at visit 2 did significantly predict depressive symptoms. After removing the non-significant covariates, circulating pro-inflammatory cytokines were still not significantly associated with depressive symptoms (*B* = -0.135, *p* = .608). Sex (*B* = 3.839, *p* = .012), sleep quality at visit 2 (*B* = 1.498, *p* < .001) and physical activity at visit 2 (*B* = -0.048, *p* = .011) remained significant predictors. Results of these regression analyses are presented in Table 16.

At visit 1, no significant association was observed between circulating cytokines and MetS symptom severity (*B* = -0.015, *p* = .539); sleep quality (*B* = -0.010, *p* = .729), physical activity (*B* < 0.001, *p* = .861), and perceived stress (*B* = -0.007, *p* = .720) were also not significantly associated with MetS symptom severity in this model. Because no variables were significant, no further models were constructed. Circulating pro-inflammatory cytokines were not significantly associated with MetS symptom severity at visit 2 (*B* = 0.043, *p* = .079). None of the covariates were significant in this model: sleep quality (*B* = -0.013, *p* = .650), physical activity (*B* < -0.001, *p* = .882), nor perceived stress (*B* = -0.008, *p* = .709). No further models were constructed due to all variables being non-significant. Results of these regression analyses are presented in Table 17.

Table 16: Results of Regression Analyses Testing the Association between Circulating Cytokines and Depressive Symptoms at Each Visit

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 13: Test whether circulating cytokines predict depressive symptoms at visit 1, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 91)			
Circulating cytokines	-0.191 (0.243)	.435	0.375 (0.3339
Sex	1.026 (1.409)	.468	--
BMI	-0.107 (0.187)	.569	--
Sleep quality	1.311 (0.300)	**<.001***	--
Physical activity	-0.028 (0.015)	.057	--
Perceived stress	0.635 (0.206)	**.003***	--
Model 14: Test whether circulating cytokines predict depressive symptoms at visit 1, removing non-significant covariates (df=95)			
Circulating cytokines	-0.181 (0.244)	.460	0.335 (0.314)
Sleep quality	1.211 (0.298)	**.001***	--
Perceived stress	0.735 (0.188)	**<.001***	--
Model 15: Test whether circulating cytokines predict depressive symptoms at visit 2, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 91)			
Circulating cytokines	-0.079 (0.270)	.770	0.308 (0.261)
Sex	3.884 (1.549)	**.014***	--
BMI	-0.216 (0.231)	.351	--
Sleep quality	1.494 (0.311)	**<.001***	--
Physical activity	-0.045 (0.019)	**.020***	--
Perceived stress	0.095 (0.227)	.675	--
Model 16: Test whether circulating cytokines predict depressive symptoms at visit 2, removing non-significant covariates (df = 92)			
Circulating cytokines	-0.135 (0.263)	.608	0.300 (0.269)
Sex	3.839 (1.498)	**.012***	--
Sleep quality	1.498 (0.307)	**<.001***	--
Physical activity	-0.048 (0.019)	**.011***	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; BMI, body mass index; $^{*}p < .05$

Table 17: Results of Regression Analyses Testing the Association between Circulating Cytokines and Metabolic Syndrome (MetS) Symptom Severity at Each Visit

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 17: Test whether circulating cytokines predict MetS symptom severity at visit 1, with sleep quality, physical activity, and perceived stress included as covariates (df = 93)			
Circulating cytokines	0.015 (0.405)	.539	0.005 (-0.037)
Sleep quality	-0.010 (0.030)	.729	--
Physical activity	<0.001 (0.001)	.861	--
Perceived stress	-0.007 (0.019)	.720	--
Model 18: Test whether circulating cytokines predict MetS symptom severity at visit 2, with sleep quality, physical activity, and perceived stress included as covariates (df = 83)			
Circulating cytokines	0.043 (0.455)	.079	0.045 (<-0.001)
Sleep quality	-0.013 (0.029)	.650	--
Physical activity	<0.001 (0.002)	.882	--
Perceived stress	0.008 (0.020)	.709	--

Note. SE, standard error; df, degrees of freedom; MetS, metabolic syndrome

In the regression models, *ex vivo* stimulated cytokine production was not associated with depressive symptoms at visit 1 (B = -0.108, p = .704). Sex (B = 0.925, p = .525), BMI (B = -0.107, p = .573), and physical activity (B = -0.028, p = .067) at visit 1 were also not significant predictors of depressive symptoms. Sleep quality (B = 1.283, p < .001) and perceived stress (B = 0.657, p = .002) at visit 1, however, were significantly associated with depressive symptoms. After removing the non-significant covariates, *ex vivo* stimulated cytokine production was still not significantly associated with depressive symptoms (B = -0.274, p = .311), while sleep quality (B = 1.207, p < .001) and perceived stress (B = 0.739, p = .001) at visit 1 remained significant predictors. At visit 2, *ex vivo* stimulated cytokine production was again not associated with depressive symptoms (B = 0.224, p = .481), nor was BMI at visit 2 (B = -0.230, p = .312) or perceived stress at visit 2 (B = 0.092, p = .686). Sex (B = 4.063, p = .011), sleep quality at visit 2 (B = 1.532, p < .001), and physical activity at visit 2 (B = -0.046, p = .017) were significant predictors of depressive symptoms at visit 2. After removing the non-significant covariates, stimulated cytokine production was still not a significant predictor of depressive symptoms (B = 0.230, p = .467). Sex (B = 4.014, p = .009), sleep quality (B = 1.551, p < .001), and physical

activity (*B* = -0.046, *p* = .017) at visit 2 remained significant predictors of depressive symptoms. Results of these regression analyses are presented in Table 18.

Table 18: Results of Regression Analyses Testing the Association between Stimulated Cytokines and Depressive Symptoms at Each Visit

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 19: Test whether stimulated cytokines predict depressive symptoms at visit 1, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 91)			
Stimulated cytokines	-0.108 (0.283)	.704	0.372 (0.331)
Sex	0.925 (1.450)	.525	--
BMI	-0.107 (0.189)	.573	--
Sleep quality	1.283 (0.298)	**<.001***	--
Physical activity	-0.028 (0.015)	.067	--
Perceived stress	0.657 (0.205)	**.002***	--
Model 20: Test whether stimulated cytokines predict depressive symptoms at visit 1, removing non-significant covariates (df = 95)			
Stimulated cytokines	-0.274 (0.269)	.311	0.339 (0.318)
Sleep quality	1.207 (0.296)	**<.001***	--
Perceived stress	0.739 (0.187)	**.001***	--
Model 21: Test whether stimulated cytokines predict depressive symptoms at visit 2, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 88)			
Stimulated cytokines	0.224 (0.317)	.481	0.311 (0.264)
Sex	4.063 (1.56)	**.011***	--
BMI	-0.230 (0.226)	.312	--
Sleep quality	1.532 (0.303)	**<.001***	--
Physical activity	-0.046 (0.019)	**.017***	--
Perceived stress	0.092 (0.226)	.686	--
Model 22: Test whether stimulated cytokines predict depressive symptoms at visit 2, removing non-significant covariates (df = 90)			
Stimulated cytokines	0.230 (0.315)	.467	0.302 (0.271)
Sex	4.014 (1.510)	**.009***	--
Sleep quality	1.551 (0.299)	**<.001***	--
Physical activity	-0.049 (0.019)	**.009***	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; BMI, body mass index; $^*p < .05$

In the regression models, at visit 1, *ex vivo* stimulated cytokine production was not a significant predictor of MetS symptom severity (*B* = 0.033, *p* = .236). None of the covariates were significantly associated with MetS symptom severity in this model: sleep quality (*B* = 0.010, *p* = .734), physical activity (*B* < 0.001, *p* = .988), or perceived stress (*B* = -0.007, *p* = .716) at visit 1. Because all covariates were not significant, no additional models were constructed. Results were similar at visit 2. *Ex vivo* stimulated cytokine production was not significantly associated with MetS symptom severity (*B* = 0.041, *p* = .226). No covariates were

significant predictors of MetS symptom severity in this model: sleep quality (*B* = -0.019, *p* = .550), physical activity (*B* = -0.001, *p* = .496), or perceived stress (*B* = -0.009, *p* = .720) at visit 2. Because all covariates were not significant, no additional models were constructed. Results of these regression analyses are presented in Table 19.

Table 19: Results of Regression Analyses Testing the Association between Stimulated Cytokines and Metabolic Syndrome (MetS) Symptom Severity at Each Visit

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 23: Test whether stimulated cytokines predict MetS symptom severity at visit 1, with sleep quality, physical activity, and perceived stress included as covariates (df = 93)			
Stimulated cytokines	0.033 (0.027)	.236	0.016 (-0.026)
Sleep quality	-0.010 (0.030)	.734	--
Physical activity	<0.001 (0.001)	.988	--
Perceived stress	0.007 (0.019)	.716	--
Model 24: Test whether stimulated cytokines predict MetS symptom severity at visit 2, with sleep quality, physical activity, and perceived stress included as covariates (df = 83)			
Stimulated cytokines	0.020 (0.030)	.511	0.010 (-0.034)
Sleep quality	-0.011 (0.029)	.704	--
Physical activity	<0.001 (0.002)	.858	--
Perceived stress	0.011 (0.021)	.593	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; MetS, metabolic syndrome

Results from Hypothesis 4

Hypotheses 4a-4e. From visit 1 to visit 2 (i.e., across the first semester of college): 4a) diet quality would decline, while 4b) circulating cytokines, 4c) ex vivo stimulated cytokine production, 4d) depressive symptoms, and 4e) MetS symptom severity would increase.

Results of paired t-tests showed that diet quality declined significantly across the semester (mean change = -3.093; 95% CI = -5.362, -0.823; *p* = .008), indicating that diet quality got worse. MetS symptom severity increased significantly across the semester (mean change = 0.152; 95% CI = 0.085, 0.219; *p* < .001), indicating that students' cardiometabolic health got worse. Circulating cytokines (mean change = 0.102; 95% CI = -0.679, 0.883; *p* = .769), stimulated cytokine production (mean change = 0.155; 95%CI = -0.656, 0.346; *p* = .540), and depressive symptoms (mean change = 0.518; 95% CI = -0.625, 1.661; *p* = .371) did not decline significantly across the semester. Results of these comparisons are presented in Table 20.

Table 20: Results of t-tests Comparing Measures taken at Visit 1 and Visit 2

	Mean (*SD*) at visit 1	Mean (*SD*) at visit 2	Mean change	*t* (df)	*p*
Diet quality	53.81 (12.53)	50.46 (13.77)	- 3.093	-2.702 (106)	**.008***
Circulating cytokines	0.36 (2.66)	-0.57 (2.92)	0.102	0.260 (89)	.796
Stimulated cytokines	0.03 (2.40)	0.08 (2.40)	-0.155	-0.616 (89)	.540
Depressive symptoms	8.38 (7.80)	8.90 (8.55)	0.518	-0.898 (109)	.371
MetS symptom severity	-0.41 (0.67)	-0.27 (0.70)	0.152	4.482 (100)	**<.001***

Note. SD, standard deviation; df, degrees of freedom; MetS, metabolic syndrome; * $p < .05$

Results from Hypothesis 5

Hypotheses 5a-5d. Larger decreases in diet quality between visit 1 and visit 2 would be associated with 5a) higher levels of circulating cytokines, 5b) higher levels of cytokine production in response to *ex vivo* stimulation with LPS, 5c) heightened depressive symptoms, and 5d) worse MetS symptom severity at visit 2.

In the regression models, change in diet quality was not a significant predictor of circulating cytokines at visit 2 (B = -0.034, p = .232); sex (B = 0.094, p = .879), physical activity at visit 2 (B = -0.005, p = .488), and perceived stress at visit 2 (B = -0.065, p = .479) were also not significant predictors in this model. BMI at visit 2 (B = 0.187, p = .042) and sleep quality at visit 2 (B = -0.254, p = .038) were significantly associated with circulating cytokines at visit 2 and were retained as covariates. After removing the non-significant covariates, the association between change in diet quality and circulating cytokines at visit 2 remained non-significant (B = -0.032, p = .237), while BMI at visit 2 (B = 0.193, p = .031) and sleep quality at visit 2 (B = -0.255, p = .033) remained significant. Results of this regression analysis are presented in Table 21.

Change in diet quality was also not associated with *ex vivo* stimulated cytokine production at visit 2 (B = 0.002, p = .925). No covariates were significant in this model: sex (B = -0.748, p = .169), BMI at visit 2 (B = 0.003, p = .970), sleep quality at visit 2 (B = -0.083, p = .430), physical activity at visit 2 (B = 0.007, p = .267), nor perceived stress at visit 2 (B = 0.040, p = .618). Because no covariates were significant, no further models were constructed. Results of this regression analysis are presented in Table 22.

Table 21: Results of Regression Analyses Testing whether Change in Diet Quality Predicts Circulating Cytokines at Visit 2

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 25: Test whether change in diet quality predicts circulating cytokines at visit 2, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 85)			
Diet quality change	-0.034 (0.028)	.232	0.128 (0.067)
Sex	0.094 (0.620)	.880	--
BMI	0.187 (0.090)	**.042***	--
Sleep quality	-0.254 (0.120)	**.038***	--
Physical activity	-0.005 (0.008)	.488	--
Perceived stress	-0.065 (0.091)	.479	--
Model 26: Test whether change in diet quality predicts circulating cytokines at visit 2, removing non-significant covariates (df = 89)			
Diet quality change	-0.032 (0.027)	.237	0.113 (0.083)
BMI	0.193 (0.088)	**.031***	--
Sleep quality	-0.255 (0.118)	**.033***	--

Note. SE, standard error; df, degrees of freedom; adj, adjusted; BMI, body mass index;
* $p < .05$

Table 22: Results of Regression Analysis Testing whether Change in Diet Quality predicts Stimulated Cytokines at Visit 2

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 27: Test whether change in diet quality predicts stimulated cytokines at visit 2, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 91)			
Diet quality change	0.002 (0.024)	.925	0.039 (-0.028)
Sex	-0.748 (0.540)	.169	--
BMI	0.003 (0.079)	.970	--
Sleep quality	-0.083 (0.105)	.430	--
Physical activity	0.007 (0.007)	.267	--
Perceived stress	0.040 (0.079)	.618	--

Note. SE, standard error; df, degrees of freedom; adj, adjusted; BMI, body mass index

Change in diet quality did not significantly predict depressive symptoms at visit 2 (B = -0.085, p = .164); BMI at visit 2 (B = -0.150, p = .449) and perceived stress at visit 2 (B = 0.271, p = .177) were also not significant in this model. Sex (B = 4.200, p = .005), sleep quality at visit 2 (B = 1.414, p = .016), and physical activity at visit 2 (B = -0.044, p = .016) were significant predictors of depressive symptoms at visit 2. After removing the non-significant covariates, results were similar: change in diet quality was still not significantly associated with depressive symptoms (B = -0.080, p = .186), while sex (B = 4.661, p = .001), sleep quality at visit 2 (B =

1.458, $p < .001$), and physical activity at visit 2 ($B = 0.048$, $p = .008$) remained significant.

Results of this analysis are presented in Table 23.

Table 23: Results of Regression Analyses Testing whether Change in Diet Quality Predicts Depressive Symptoms at Visit 2

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 28: Test whether change in diet quality predicts depressive symptoms at visit 2, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 99)			
Diet quality change	-0.085 (0.060)	.164	0.325 (0.284)
Sex	4.200 (1.466)	**.005***	--
BMI	-0.150 (0.197)	.449	--
Sleep quality	1.414 (0.280)	**<.001***	--
Physical activity	-0.044 (0.018)	**.016***	--
Perceived stress	0.271 (0.199)	.177	--
Model 29: Test whether change in diet quality predicts depressive symptoms at visit 2, removing non-significant covariates (df = 101)			
Diet quality change	-0.080 (0.060)	.186	0.310 (0.282)
Sex	4.661 (1.422)	**.001***	--
Sleep quality	1.458 (0.279)	**<.001***	--
Physical activity	-0.048 (0.018)	**.008***	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; BMI, body mass index;
* $p < .05$

Finally, change in diet quality did not predict MetS symptom severity at visit 2 ($B = -0.001$, $p = .826$). No covariates were significant in this model: sleep quality at visit 2 ($B = 0.005$, $p = .852$), physical activity at visit 2 ($B < 0.001$, $p = .910$), nor perceived stress at visit 2 ($B = 0.017$, $p = .389$). Because no covariates were significant, no further models were constructed.

Results of this regression analysis are presented in Table 24.

Table 24: Results of Regression Analysis Testing whether Change in Diet Quality Predicts Metabolic Syndrome (MetS) Symptom Severity at Visit 2

	B (*SE*)	*p*	R^2 (adj. R^2)
Model 30: Test whether change in diet quality predicts MetS symptom severity at visit 2, with sex, BMI, sleep quality, physical activity, and perceived stress included as covariates (df = 102)			
Diet quality change	-0.001 (0.006)	.826	0.008 (-0.031)
Sleep quality	-0.005 (0.028)	.852	--
Physical activity	<0.001 (0.002)	.910	--
Perceived stress	0.017 (0.019)	.389	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; BMI, body mass index; MetS, metabolic syndrome

Results of Exploratory Analyses

Given that overall diet quality was significantly associated with MetS symptom severity, exploratory analyses were conducted to determine whether or not components of diet quality (e.g., total vegetables; added sugars) predicted MetS symptom severity. For these analyses, unadjusted Pearson correlations among individual HEI-2015 components and MetS symptom severity concurrently at each visit were examined. Then, multiple linear regression was used to assess whether specific components of the HEI-2015 scores significantly predict MetS symptom severity concurrently at each visit. All 13 of the HEI-2015 components were included as predictors in each model; separate models were constructed for each study visit.

Correlational analyses indicated that total fruits (r = -.349, p < .001), whole fruits (r = -.362, p < .001), total vegetables (r = -.370, p < .001), greens and beans (r = -.263, p = .006), whole grains (r = -.212, p = .029), and seafood and plant protein (r = -.241, p = .013) were all significantly associated with MetS symptom severity at visit 1. The correlation between added sugars and MetS symptom severity approached, but did not reach, significance at visit 1 (r = -.181, p = .063). Conversely, dairy (r = -.030, p = .759), total protein (r = .030, p = .761), the fatty acid ratio (r = -.037, p = .706), refined grains (r = -.131, p = .180), sodium (r = .016, p = .873), and saturated fat (r = -.124, p = .205) were not significantly correlated with MetS symptom severity at visit 1. Results of these analyses are presented in Table 25.

Correlational analyses found that total fruits (r = -.275, p = .006), whole fruits (r = -.270, p = .007), total vegetables (r = -.324, p = .001), whole grains (r = -.310, p = .002), seafood and plant protein (r = -.302, p = .002) and the fatty acid ratio (r = -.270, p = .007), were also significantly associated with MetS symptom severity at visit 2. Consumption of greens and beans (r = -.191, p = .058) was not significantly associated with MetS symptom severity at visit 2, despite being significantly associated at visit 1. Additionally, added sugars (r = -.236, p = .018), and saturated fat (r = -.279, p = .005) and MetS symptom severity were significantly associated with MetS symptom severity at visit 2, despite not being significantly associated at visit 1. Consumption of dairy (r = -.076, p = .457), total protein (r = -.007, p = .939), refined

grains (*r* = -.046, *p* = .650), and sodium (*r* = -.047, *p* = .643), were not associated with MetS symptom severity at visit 2. Results of these analyses are presented in Table 26.

Table 25: Correlations between Components of Diet Quality and Metabolic Syndrome (MetS) Symptom Severity at Visit 1

Component	*r*	*p*
Total fruits	-.349	**<.001***
Whole fruits	-.362	**<.001***
Total vegetables	-.370	**<.001***
Greens and beans	-.263	**.006***
Whole grains	-.212	**.029***
Dairy	-.030	.759
Total Protein	-.030	.761
Seafood and plant protein	-.241	**.013***
Fatty acid ratio	-.037	.706
Refined grains	-.131	.180
Sodium	-.016	.873
Added sugars	-.181	.063
Saturated fat	-.124	.205

Note. 104 degrees of freedom; * *p* < .05

Table 26: Correlations between Components of Diet Quality and Metabolic Syndrome (MetS) Symptom Severity at Visit 2

	r	p
Total fruits	-.275	**.006***
Whole fruits	-.270	**.007***
Total vegetables	-.324	**.001***
Greens and beans	-.191	.058
Whole grains	-.310	**.002***
Dairy	.076	.457
Total protein	-.007	.939
Seafood and plant protein	-.302	**.002***
Fatty acid ratio	-.270	**.007***
Refined grains	-.046	.650
Sodium	-.047	.643
Added sugars	-.236	**.018***
Saturated fat	-.279	**.005***

Note. 97 degrees of freedom; * *p* < .05

Results of the regression analysis indicate that total vegetables (*B* = -0.129, *p* = .026) were significantly associated with MetS symptom severity at visit 1. Total fruits (*B* = -0.026, *p* = .716), whole fruits (*B* = -0.076, *p* = .204), greens and beans (*B* = 0.010, *p* = .804), dairy (*B* = -

0.012, *p* = .660), total protein (*B* = 0.016, *p* = .810), seafood and plant protein (*B* = -0.022, *p* = .571), fatty acid ratio (*B* = 0.008, *p* = .798), refined grains (*B* = -0.017, *p* = .485), sodium (*B* = 0.010, *p* = .726), added sugars (*B* = -0.021, *p* = .543), and saturated fat (*B* = -0.013, *p* = .695) were not significantly associated with MetS symptom severity in this model. Results of this regression analysis are presented in Table 27.

At visit 2, results of the regression analysis indicate that seafood and plant protein (*B* = -0.087, *p* = .022) was significantly associated with MetS symptom severity. Total fruits (*B* = -0.054, *p* = .484), whole fruits (*B* = -0.014, *p* = .833), total vegetables (*B* = -0.079, *p* = .229), greens and beans (*B* = 0.007, *p* = .856), dairy (*B* = 0.016, *p* = .581), total protein (*B* = -0.051, *p* = .344), the fatty acid ratio (*B* = -0.022, *p* = .544), refined grains (*B* = 0.026, *p* = .238), sodium (*B* = -0.008, *p* = .786), added sugars (*B* = -0.061, *p* = .070), and saturated fat (*B* = -0.011, *p* = .749) were not significantly associated with MetS symptom severity in this model. Results of this regression analysis are presented in Table 28.

Table 27: Results of Regression Analysis Testing whether Components of Diet Quality are associated with Metabolic Syndrome (MetS) Symptom Severity at Visit 1

	B (*SE*)	*p*	R^2 (adj. R^2)
Total fruits	-0.026 (0.071)	.716	0.273 (0.170)
Whole fruits	-0.076 (0.059)	.204	--
Total vegetables	-0.129 (0.057)	**.026***	--
Greens and beans	0.010 (0.041)	.804	--
Whole grains	-0.028 (0.022)	.209	--
Dairy	-0.012 (0.027)	.660	--
Total protein	0.016 (0.065)	.810	--
Seafood and plant protein	-0.022 (0.039)	.571	--
Fatty acid ratio	0.008 (0.030)	.798	--
Refined grains	-0.017 (0.024)	.485	--
Sodium	0.010 (0.028)	.726	--
Added sugars	-0.021 (0.034)	.543	--
Saturated fat	-0.013 (0.033)	.695	--

Note. 92 degrees of freedom; * $p < .05$

Table 28: Results of Regression Analysis Testing whether Components of Diet Quality are associated with Metabolic Syndrome (MetS) Symptom Severity at Visit 2

	B (*SE*)	*p*	R^2 (adj. R^2)
Total fruits	-0.054 (0.077)	.484	0.315 (0.210)
Whole fruits	0.014 (0.067)	.833	--
Total vegetables	-0.079 (0.065)	.229	--
Greens and beans	0.007 (0.039)	.856	--
Whole grains	-0.038 (0.021)	.075	--
Dairy	0.016 (0.029)	.581	--
Total protein	0.051 (0.053)	.344	--
Seafood and plant protein	-0.087 (0.037)	**.022***	--
Fatty acid ratio	-0.022 (0.036)	.544	--
Refined grains	0.026 (0.022)	.238	--
Sodium	-0.008 (0.029)	.786	--
Added sugars	-0.061 (0.033)	.070	--
Saturated fat	-0.011 (0.034)	.749	--

Note. 85 degrees of freedom; * $p < .05$

Because diet quality was found to change significantly across the semester, exploratory t-tests were used to examine mean differences in HEI-2015 components from visit 1 to visit 2. Because caloric intake varies by sex, with males typically consuming more calories per day (Rolls et al., 1991), daily caloric intake was also examined for males and females separately. Daily caloric intake significantly decreased in the total sample (mean change = -585 kcal, p = .008). Among males, the daily caloric intake between visit 1 and visit 2 was significant (mean change = -854 kcal; p = .031); however, the change was not significant among females (mean change = -421 kcal; p = .112). Whole grain consumption was the only HEI-2015 component to change significantly (mean change = -0.711, p = .041), with consumption decreasing across the semester. The change in consumption of total fruit (mean change = -0.274, p = .157), whole fruit (mean change = -0.311, p = .185), total vegetable (mean change = -0.248, p = .079), total protein (mean change = -0.052, p = .676), seafood and plant protein (mean change = -0.260, p = .262), and added sugars (mean change = 0.376, p = .110) was not significant, though these components worsened nominally. Consumption of greens and beans (mean change = 0.173, p = .472), dairy (mean change = 0.117, p = .727), refined grains (mean change = -0.624, p =

.124), sodium (mean change = -0.205, p = .366), and saturated fat (mean change = -0.612, p = .099) also did not change significantly across the semester, although these components nominally improved. Results of these exploratory analyses are presented in Table 29.

Table 29: Results of t-tests Comparing Components of Diet Quality at Visit 1 and Visit 2

	Mean (*SD*) at visit 1	Mean (*SD*) at visit 2	Mean change	*t* (df)	*p*
Daily kcal	5477 (2227)	5029 (2140)	-585	-2.701 (99)	**.008***
Male	6172 (2227)	5467 (2298)	-854	-2.245 (39)	**.031***
Female	5016 (2203)	4731 (2007)	-421	-1.615 (58)	.112
Total Fruit	2.40 (1.83)	2.15 (1.86)	-0.274	-1.426 (100)	.157
Whole fruits	2.94 (2.13)	2.68 (2.17)	-0.311	-1.333 (100)	.185
Total vegetables	3.00 (1.35)	2.71 (1.42)	-0.248	-1.775 (100)	.079
Greens and beans	2.1 (2.1)	2.25 (2.19)	0.173	0.722 (100)	.472
Whole grains	4.17 (3.18)	3.45 (3.3)	-0.711	-2.071 (100)	**.041***
Dairy	6.11 (2.75)	6.16 (2.79)	0.117	0.350 (100)	.727
Total Protein	3.81 (3.46, 4.22) [a]	4.06 (1.38)	-0.052	-0.419 (100)	.676
Seafood and plant protein	2.76 (1.37)	2.62 (2.05)	-0.260	-1.127 (100)	.262
Fatty acid ratio	4.61 (3.48)	4.16 (3.41)	-0.375	-0.920 (100)	.360
Refined grains	5.55 (3.3)	4.9 (3.43)	-0.624	-1.553 (100)	.124
Sodium	4.09 (3.0)	4.03 (2.99)	-0.205	-0.908 (100)	.366
Added sugars	7.35 (2.4)	7.63 (2.46)	0.376	1.612 (100)	.110
Saturated fat	4.60 (2.99)	4.02 (3.33)	-0.612	-1.665 (100)	.099

Note. SD, standard deviation; df, degrees of freedom; kcal, kilocalories; * p < .05

Finally, because MetS symptom severity was found to significantly decline across the semester, exploratory t-tests were conducted to test for mean differences in each component of MetS across the semester. The specific components included in the ATP-III criteria for MetS and the MetS symptom severity equations vary slightly; the MetS severity score substitutes BMI for waist circumference to improve the clinical utility of the score (Gurka et al., 2012). Thus, comparisons for both BMI and waist circumference were included in the present study. Additionally, because weight gain in the first year of college is an important and commonly explored endpoint in existing scientific literature (e.g., D. A. Anderson et al., 2003; Jung et al., 2008; Ludy et al., 2018; Mihalopoulos et al., 2008) change in weight was also explored. Results indicate that waist circumference significantly increased across the semester (mean change = 1.4 cm, p < .001), as did BMI (mean change = 0.6 kg/m^2, p < .001), and body weight (mean change =1.4 kg, p < 0.001); HDL cholesterol decreased (i.e., got worse) significantly across the

semester (mean change = -1.747 mg/dL, p = .030). Triglycerides (mean change = 11.118 mg/dL, p < .001) and systolic blood pressure (mean change = 2 mmHg, p = .005) increased (i.e., got worse) significantly across the semester. Diastolic blood pressure (mean change = 1 mmHg, p = .180) and fasting blood glucose (mean change = 0.824 mg/dL, p = .302) did not significantly change. Results of these exploratory analyses are presented in Table 30.

Table 30: Results of t-tests Comparing Metabolic Syndrome (MetS) Components at Visit 1 and Visit 2

	Mean (*SD*) at visit 1	Mean (*SD*) at visit 2	Mean change	*t* (df)	*p*
Waist (cm)	77.2 (10.2)	78.7 (9.8)	1.4	5.049 (102)	**<.001***
BMI (kg/m^2)	23.5 (3.7)	24.1 (3.6)	0.6	3.562 (109)	**<.001***
Weight (kg)	69.1 (13.2)	70.3 (13.0)	1.4	4.233 (102)	**<.001***
HDL (mg/dL)	57.4 (12.4)	55.6 (12.8)	-1.7	-2.196 (101)	**.030***
TG (mg/dL)	81.0 (30.1)	90.6 (40.5)	11.1	4.275 (101)	**<.001***
SBP (mmHg)	109 (10)	111 (90)	2	2.890 (102)	**.005***
DBP (mmHg)	62 (6)	63 (6)	1	1.351 (102)	.180
Glucose (mg/dL)	91.2 (7.0)	92.2 (7.1)	0.8	1.038 (101)	.302

Note. SD, standard deviation; df, degrees of freedom; BMI, body mass index; HDL, high-density lipoprotein; TG, triglycerides; SBP, systolic blood pressure; DBP, diastolic blood pressure;
* p < .05

Chapter 5: Discussion

Diet Quality is Significantly Associated with Metabolic Syndrome Symptom Severity in First-Semester College Students

Results of the present study suggest that poorer diet quality is significantly and robustly associated with increased MetS symptom severity in first-year college students, supporting Hypothesis 1b. Students' diet quality scores were negatively correlated with MetS symptom severity at both visits; the strength of the correlation was moderate at both visit 1 and at visit 2. The association remained significant when diet quality was included as a predictor of MetS symptom severity in regression models with covariates included. Thus, across two visits and several analyses, results indicate that poorer diet quality is associated with concurrently poorer cardiometabolic health in first-semester college students. This finding adds to growing body of literature indicating that diet quality is an important factor in maintaining cardiometabolic health (Dahm et al., 2016; Morze et al., 2020; Neuenschwander et al., 2019; Schwingshackl & Hoffmann, 2015; Sotos-Prieto et al., 2015). Additionally, past primary prevention research has often been hampered by the lack of measures sensitive enough to detect disease risk prior to disease onset (Alagona & Ahmad, 2015; Gilstrap & Wang, 2012). The present study was not designed to assess long-term disease risk, and consequently it cannot be concluded that the MetS symptom severity score used would necessarily predict disease outcomes in this sample. However, because diet quality and MetS are associated in adults (e.g., Harrison et al., 2020), the present parallel finding of an association between diet quality and the MetS symptom severity score provides evidence that this score may be a useful tool for risk assessment in primary prevention research with pre-clinical samples. The participants in this study were all young adults (18 to 19 years old), the vast majority of whom did not meet full MetS criteria at either time point. However, higher MetS symptom severity earlier in life has been associated with increased risk of developing MetS, CVD, and T2D in adulthood (DeBoer et al., 2016; Koskinen et al., 2017). Thus, the present finding that diet quality is associated with MetS

symptom severity in first-semester college students could help inform the development of primary prevention programs aimed at lifestyle-based cardiometabolic disease prevention in young individuals.

These results also parallel existing research examining the association between the MetS symptom severity score (Gurka et al., 2012) and diet quality. Interestingly, MetS symptom severity and diet quality have both been improving among US adolescents aged 12-19 in recent years, despite BMI increasing significantly in this population (A. M. Lee et al., 2016). The decline in MetS symptom severity observed in adolescents was driven by improvements in HDL cholesterol and triglyceride levels, which were in turn associated with improvements in diet quality (A. M. Lee et al., 2016). While the present study found increasing MetS symptom severity accompanied by decreasing diet quality across time, both studies suggest that better diet quality is associated with reduced MetS symptom severity in young people. A recent study directly compared MetS symptom severity scores with HEI-2015 scores as a measure of diet quality, and found that the effect of total HEI score on MetS symptom severity was significant (β = -0.004, p = .01) (Summer et al., 2022). The effect seen by Summer and colleagues is somewhat smaller than the effect in the present study (B's = -0.022, -0.020 at visit 1 and 2, respectively; p's <0.001), possibly due to the inclusion of participants across a wider age range in their study. The present study sample consisted entirely of 18- to 19-year-old students. The published study had an upper age limit 19, but also included adolescents as young as 12 years old (Summer et al., 2022). Given that MetS is a chronic condition that develops across time, it is plausible that their sample may be more metabolically healthy than the present, and slightly older on average, study sample. The younger age of the sample may also have attenuated the association between diet quality and MetS symptom severity. However, MetS symptom severity scores were substantially higher (i.e., worse) in the published study compared to the present study (mean = -0.08, compared to -0.41 at visit 1 and -0.26 at visit 2), while diet quality was fairly similar (mean = 47.4, compared to 53.8 at visit 1 and 50.5 at visit 2).

The slightly lower diet quality observed by Summer and colleagues (2022) may also be related to their inclusion of younger participants. According to the nationally representative survey What We Eat in America (WWEIA), the dietary intake interview component of the National Health and Nutrition Examination Survey (NHANES), adolescents aged 14 to 18 have an average diet quality score of 49 out of 100 on the HEI-2015, while young adults aged 19-30 score 53 out of 100 (National Center for Health Statistics, 2017-2018 data). Thus, younger adolescents tend to consume a lower quality diet, and the inclusion of younger participants may result in lower mean diet quality scores. Given the present results, the diet quality of first semester college students at Penn State may be comparable to other Americans in the same age range. More broadly, however, the average American adult scores 58 out of 100 on the HEI (National Center for Health Statistics, 2017-2018 data). Thus, it appears that first-semester college students at Penn State may consume a poorer quality diet compared to the average American adult.

Because diet quality was significantly associated with MetS symptom severity, exploratory analyses were conducted to examine which specific components of diet quality were most predictive. Past research has reported that specific components of diet quality, such as fruits (Tian et al., 2018; Zhang & Zhang, 2018) and whole grains (H. Guo et al., 2021) may influence risk of MetS and cardiometabolic disease. However, nutrients and foods can interact with each other in complex ways that alter their physiological effects (Calder & Newsholme, 1993; Julibert et al., 2019; Kubena & McMurray, 1996). These interactions can make interpreting the effects of individual dietary components challenging, and has pushed the field of nutrition science toward a greater emphasis on dietary patterns (Arnett et al., 2019; F. B. Hu, 2002). Additionally, use of individual components over a composite score increases the number of comparisons, and therefore increases the chances of type I error (S. Chen et al., 2017). Some researchers have argued that multiple comparisons may not be problematic, particularly when using large data sets or multilevel modeling (Gelman et al., 2012; Rothman, 1990).

However, the present study had a relatively small sample size and would not be suitable for multilevel modeling; the focus was therefore on the effect of overall diet quality, rather than individual components. Exploratory analyses of the components of diet quality were included here as well, primarily to explore whether the results obtained would align with existing literature about the effects of dietary components on MetS symptoms and CVD risk.

In the present study, 6 out of the 13 HEI-2015 components (total fruits, whole fruits, total vegetables, greens and beans, whole grains, and seafood and plant protein) were significantly correlated with MetS symptom severity at both study visits. Past research has also supported an association between these elements of diet and MetS risk or symptoms (Chang et al., 2012; H. Guo et al., 2021; Hajihashemi et al., 2021; Hermsdorff et al., 2009; Karimi et al., 2020; Muriuki et al., 2021; Shang et al., 2017; Tian et al., 2018; Zhang & Zhang, 2018). However, some mixed results have been reported (e.g., Muriuki et al., 2021; Zhang & Zhang, 2018). The present study found no significant correlation between 4 dietary components (dairy, total protein, refined grains, and sodium) and MetS symptom severity at either visit. For dairy (G. C. Chen et al., 2015; Crichton et al., 2011) and total protein (Crichton et al., 2011; Shang et al., 2017), published results have been inconsistent; the role of these dietary components on MetS risk remains unclear. Existing meta-analyses generally support an association between MetS risk and consumption of refined grains (H. Guo et al., 2021) and sodium (Soltani et al., 2019), in contrast to the present findings.

Across the two study visits, different results were found for added sugars, fatty acid ratio, and saturated fat, and for total vegetables in the correlational analyses, as well as for seafood and plant protein in the regression analyses. It is likely that collinearity impacted the regression results, as individuals with healthy or unhealthy overall diet patterns are likely to have correlated scores for individual components (Kourlaba & Panagiotakos, 2009). Still, published studies have also produced inconsistent findings. For example, added sugar consumption may or may not significantly impact MetS risk (Rippe & Angelopoulos, 2015; Rodríguez et al., 2016). Existing

evidence suggests that reducing the dietary fatty acid ratio (i.e., consuming more unsaturated fatty acids and less saturated fatty acids) may protect against MetS, but the effect varies depending on what specific foods and nutrients are used to replace the saturated fatty acids (Julibert et al., 2019). Beyond this, each diet quality component is composed of a diverse array of foods, and the effect of a component on cardiometabolic health may vary depending on the types of foods and nutrients being consumed. While higher saturated fat consumption is generally linked to increased MetS risk, the effect may vary depending on the specific saturated fatty acids being consumed (Harrison et al., 2020; A. L. Unger et al., 2019). It is certainly plausible that dietary individual components and nutrients may uniquely influence MetS risk. However, given the inconsistent results observed, research aimed at examining specific elements of diet quality should be carefully considered, with clear *a priori* hypotheses to reduce the potential for type I error. Composite measures of diet quality, such as HEI scores, may yield more accurate results (Kourlaba & Panagiotakos, 2009), especially in studies with small samples and/or few time points.

Diet Quality Declined Significantly across the First Semester in College

Diet quality declined significantly across the semester, from a mean of 53.81 at visit 1 to a mean of 50.46 at visit 2, supporting Hypothesis 4a. While these numeric HEI-2015 scores are considered to be of paramount importance, an intuitive letter-based grading system for HEI-2015 scores has also been suggested, which is analogous to scoring used in academic classes. In this system, scores of 90 or above are considered an A; scores of 0 to 59 are an F, or essentially failing to achieve a healthy diet (Krebs-Smith et al., 2018). Present results indicate that first-year students at Penn State failed to meet dietary recommendations even at the beginning of their first semester, and got further from meeting guidelines across time. Past research has consistently found that lower diet quality, assessed via HEI-2015 scores, is associated with greater risk of CVD and all-cause mortality (E. A. Hu et al., 2020; Panizza et al., 2018; Shan et al., 2020). For example, an analysis of data from 3 large prospective cohort

studies reported that a 25-percentile higher HEI-2015 score was associated with a 10 to 20% reduction in risk of CVD (Shan et al., 2020). The observed decrease in diet quality among first-semester college students could therefore increase long-term CVD and mortality risk, particularly if diet quality remains low across time.

Because diet quality declined significantly, exploratory paired t-tests were used to test for mean differences in each component across the two study visits. Most adequacy components declined nominally across the semester; while these changes were largely not significant, the slight decreases may have contributed to the observed decline in total diet quality. Total calories consumed per day also declined significantly in the present sample. Declining caloric intake and increasing weight in the absence of physical activity changes may appear paradoxical. However, this finding adds to a growing body of literature suggesting that calories from different food sources may have different effects on weight status (Buchholz & Schoeller, 2004). Thus, diet quality may be a stronger predictor of weight status than caloric intake. Underscoring this, total daily caloric intake among children has remained stable across time in the US, while body weight and BMI have increased (Nicklas et al., 2001). Interestingly, the macronutrient profile of children's diet has improved, and energy intake per kilogram of body weight has decreased. Despite these apparently positive dietary trends, weight, BMI, and childhood obesity rates have been increasing; declining diet quality appears to be an important factor driving weight gain in American children and adolescents (Nicklas et al., 2001). The present study expands upon these findings to suggest that declining diet quality, rather than increasing caloric intake, may drive weight gain in first-semester college students as well.

Among diet quality components, the only significant change observed across the first semester in college was in whole grain consumption, which declined from a mean of 4.17 at visit 1 to a mean of 3.45 at visit 2 (p = .041). The maximum score for whole grain consumption is 5, and can be achieved by consuming ≥1.5 oz equivalents of whole grains per 1,000 calories consumed per day (Krebs-Smith et al., 2018); for reference, ¾ cup of whole grain rice is

approximately 1.5 oz equivalents of whole grains. Given that the vast majority of study participants live on campus and have campus meal plans, declining whole grain consumption and diet quality across the first semester could potentially be offset by campus policy changes. Policies aimed at replacing refined grain food products in the dining halls with whole grain versions of the same products might help improve whole grain consumption in students, and enable more students to meet dietary recommendations. However, because overall diet quality was low at both time points, more comprehensive changes to campus food policies should be considered. Surprisingly little research has specifically investigated campus food policies in colleges and universities. Still, existing evidence suggests that the quality of the campus food environment is low on average, and that healthy food items are both less available and more expensive than unhealthy items (Pulz et al., 2017; Roy et al., 2019). Students have reported that the healthfulness of food products is an important to them, but the high cost and low availability of healthy foods are deterrents (Roy et al., 2019). Nearly 80% of students responded that they wanted healthier food options provided in campus food outlets, and 52% reported that they would like visual information about how to make healthier food choices on campus (Roy et al., 2019). Thus, students appear to have an appetite for access to affordable healthy food options that is not being met by campus food outlets. Policies that enable students to make healthy choices, such as reducing the prices of healthy food options and providing clear nutrition labels on dining hall foods, could be beneficial. Some campus dining facilities at Penn State serve food buffet style, in which case there is no cost discrepancy between healthy and unhealthy food items. For these facilities, ensuring that healthy food options and nutrition information are prominently displayed may help encourage better food choices (Bassett et al., 2008; Cameron et al., 2016).

Metabolic Syndrome Symptom Severity Increased Significantly across the First Semester in College

Metabolic syndrome (MetS) symptom severity was found to increase (i.e., get worse) significantly across the first semester in the present study, supporting hypothesis 4e. The MetS symptom severity score can be interpreted as a z-score, with a mean of 0 and each unit being equal to one standard deviation; higher scores indicate worse MetS symptom severity (Gurka et al., 2012). The present study sample had a mean MetS symptom severity score of -0.41 at visit 1, suggesting that the incoming first-year students had better cardiometabolic health compared to the NHANES sample with which the score was developed (Gurka et al., 2012). By the end of the study, students' MetS symptom severity score had increased by 0.15 on average, to a score of -0.27. The MetS symptom severity score is fairly novel, but several studies supporting the clinical utility of the measure have been published (Deboer et al., 2015; DeBoer et al., 2016; Koskinen et al., 2017; A. M. Lee et al., 2017; Magnussen et al., 2016; Wang et al., 2018). Past research has found that MetS symptom severity is associated with concurrent markers of cardiovascular risk in adolescents aged 12 to 20 years (A. M. Lee et al., 2017). In a retrospective analysis of two prospective longitudinal studies, MetS symptom severity in childhood was associated with increased risk of T2D and CVD over 11.2 years, with odds ratios between 3.4 - 5.6 across models (DeBoer et al., 2016). Similarly, a retrospective analysis of over 5,800 participants from four prospective cohort studies found that higher MetS symptom severity scores in childhood predicted increased risk of MetS, T2D, and high carotid-intima thickness, indicating poor vascular health, in adulthood (Koskinen et al., 2017). The increasing MetS symptom severity observed in the present sample could therefore represent meaningful increases to students' long-term disease risk. However, comparable studies of change in cardiometabolic health across the first semester of college have been yet to be published. The present study therefore provides a novel finding of significant decline in cardiometabolic health within the first semester of beginning college, adding to a growing body of literature defining the mental and physical health risks associated with the transition to college.

Because MetS symptom severity increased significantly across the semester, exploratory paired t-tests were conducted to test for mean change in individual MetS components, including waist circumference, HDL cholesterol, triglycerides, systolic blood pressure, diastolic blood pressure, and fasting blood glucose; change in BMI and body weight were also explored. The majority of these variables significantly worsened across the semester, including waist circumference, HDL cholesterol, triglycerides, systolic blood pressure, BMI, and body weight. Existing research suggests that increasing abdominal adiposity is a primary driver of MetS development (Cornier et al., 2008). Waist circumference, a measure of abdominal adiposity, increased by 1.5 cm ($p < .001$) across the study period. This increase is not only statistically significant, but clinically significant as well: a meta-analysis including over 258,000 participants found that each 1 cm increase in waist circumference is associated with a 2% increase in odds of a CVD event (e.g., myocardial infarction, stroke) (De Koning et al., 2007). A 1 cm higher waist circumference is also associated with an 8% increase in risk of T2D (Feller et al., 2010). Results were similar when examining BMI: students' BMI increased significantly across the semester, from 23.48 kg/m^2 to 24.1 kg/m^2 (mean change = +0.593, $p < .001$). Having a BMI that is 1 kg/m^2 higher is associated with a 21% increase in the relative risk of having T2D among men, and a 15% increase among women (Feller et al., 2010). Thus, the observed increase in BMI across the first semester in college may increase long-term cardiometabolic disease risk among students.

Body weight is not directly a MetS component; however, there is substantial literature on college student weight gain. To compare the results of the present study to existing literature on the topic, exploratory t-tests were conducted to examine mean differences in body weight across the two study visits. In line with existing literature, participants gained a significant amount of weight across the study period. At least two published studies have specifically examined weight change within the first semester of college. First, a Belgian study reported that students gained an average of 1 kg in the first semester (Deliens et al., 2013), a smaller

increase than that observed in the present study (1.4 kg on average). Past research suggests that a higher starting weight predicts greater weight gain across time (Votruba et al., 2014). Thus, the lower weight gain observed in Belgian students may be related to the fact that the obesity rate in Belgium is approximately 15% (De Pauw et al., 2022), much lower than the rate of 41.9% in the US (Stierman et al., 2021). A second study conducted at a university in New York state reported that students gained a statistically significant 1.5 kg in the first semester of college (D. A. Anderson et al., 2003), similar to the present finding. First-year weight gain was also significant, but students did not significantly gain weight in the second semester. These results suggest that the first semester may be a critical period for weight gain, and informed the present study design. The present results provide further evidence that significant weight gain occurs within the first semester of beginning college. Prospective longitudinal studies examining whether this first-semester weight gain meaningfully impacts students' long-term weight status and cardiometabolic health are warranted.

Significant concurrent associations between diet quality and MetS symptom severity were observed at each visit; across the semester, diet quality declined significantly while MetS symptom severity increased significantly. Despite these associations, the change in diet quality across the semester did not predict MetS symptom severity at visit 2. One plausible explanation is that multiple health behaviors declined across the semester, and that the combined effect of these declining health behaviors was increasing MetS symptom severity. For example, students in the present study also experienced a significant increase in alcoholic drink consumption across the semester, from a mean of 4.31 drinks per week to a mean of 4.93 drinks per week [t (df) = -1.99 (100); p = 0.049]. Students were asked to report alcoholic beverage consumption as part of the diet recalls, but alcohol intake is not part of the HEI-2015 score and thus should not have been a factor in the declining diet quality observed. Many other factors influence also diet quality, though, such as socioeconomic status (Darmon & Drewnowski, 2008), meal patterns (e.g., skipping breakfast) (Leech et al., 2015), and impulsivity (Lumley et al., 2016). The present

study was not able to capture all potentially relevant factors, and it is possible that these unmeasured variables influenced the results. While the present results support an association between diet quality and cardiometabolic health in first semester college students, other lifestyle factors are likely to be important for the development of MetS. Still, the observed increase in MetS symptom severity in students who are generally required to live and eat on campus underscores the need for targeted interventions and policies aimed at protecting students' cardiometabolic health.

Diet Quality was Not Associated with Depressive Symptoms

The present study adds a null finding to the growing body of research examining the association between diet quality and depressive symptoms. The association between depressive symptoms and diet quality approached, but did not reach, significance at visit 1 in both the correlational and regression analyses. At visit 2, the association between depressive symptoms and diet quality was not significant. Similarly, change in diet quality across the semester did not predict depressive symptoms at visit 2. Plausible physiological mechanisms link diet quality to depression, and some evidence suggests that the two are associated (Berk & Jacka, 2019; Lassale et al., 2019). However, past research on the associations between diet quality and depressive symptoms has yielded mixed results. Results both for (Gomes et al., 2021; Jacka, Kremer, et al., 2011; Quehl et al., 2017) and against (Winpenny et al., 2018) an association between diet quality and depression risk have been found.

It is possible that the present study may have been underpowered to detect an effect; studies showing a significant relationship between diet quality and depression often include large sample sizes of over 3,000 participants (Gomes et al., 2021; Jacka, Kremer, et al., 2011). Supporting the potential power issue, an existing study reported that diet quality and depressive symptoms were significantly associated in a sample of 141 female university students (Quehl et al., 2017), more participants than the present study, despite having a weaker effect size. However, null results have also been reported by at least one large and more adequately

powered study with over 600 participants (Winpenny et al., 2018). Further, systematic reviews and meta-analyses often report weak or inconsistent evidence across studies (S. Collins et al., 2022; Molendijk et al., 2018; Quirk et al., 2013). Much of the published research has used low-quality study designs, such as cross-sectional studies with inadequate assessment of confounding factors (S. Collins et al., 2022; Molendijk et al., 2018; Quirk et al., 2013). It is possible that confounding factors, such as socioeconomic status (Darmon & Drewnowski, 2008, 2015), may have driven the significant published results (Molendijk et al., 2018; Quirk et al., 2013; Winpenny et al., 2018). Still, repeated significant findings in large studies suggest that low diet quality may contribute to depression risk (Gomes et al., 2021; Jacka, Kremer, et al., 2011). Future prospective longitudinal studies could help elucidate whether or not diet quality plays a causal role in the development of depression.

Other studies have found that the association between diet quality and depression may depend on the measures used. A 2013 meta-analysis of 25 studies found limited evidence that diet quality was significantly associated with depression when assessed as adherence to the Mediterranean diet or to the Norwegian diet (Quirk et al., 2013). When diet quality was assessed using other measures of a healthy diet, such as HEI scores, conflicting results were observed across studies and no conclusions could be drawn. The authors acknowledge that heterogeneity in the definition of a healthy diet, as well as in measures of diet quality and depression, may drive the observed inconsistencies. While defining a healthy diet remains challenging, developing clearer definitions would help move the field forward. Additionally, it is possible that the timing of measures may have influenced the present results, as measures were collected across a period of up to two weeks for each individual at each time point. Future studies more specifically examining associations between diet quality and depressive symptoms at the day level could provide beneficial information about whether diet quality contributes to depressive symptoms experienced on the same day.

Diet Quality was Not Associated with Markers of Immune Function

While a growing body of literature suggests that diet quality may modulate immune function (Nobs et al., 2020) and predict inflammation in both children (Bujtor et al., 2021) and adults (Mattei et al., 2018), no significant association was observed between diet quality and markers of inflammation in the present study. Similarly, the change in diet quality across the semester did not predict circulating cytokines or stimulated cytokine production at visit 2. Importantly, existing findings in support of an association between diet quality and markers of immune function have had greater statistical power than the present study, such as a meta-analysis of 53 studies (Bujtor et al., 2021) and a sample of over 14,000 participants (Mattei et al., 2018). Given the complex interactions among diet components and the complexity of measuring immune function, perhaps larger sample sizes are needed in order to observe patterns in the relationship between diet and immune function. It is also possible that the present study failed to find an association between markers of inflammation and diet quality due to the measures used. For example, a recent meta-analysis reported that adherence to a high quality diet attenuated inflammation in children and adolescents aged 2-19 (Bujtor et al., 2021). The measures of a healthy diet that were significantly associated with markers of inflammation included adherence to the Mediterranean diet, adequate consumption of fruits and vegetables, and intake of certain specific nutrients, such as fiber. Among measures of an unhealthy diet, adherence to a Western dietary pattern, as well as intake of specific foods (e.g., added sugars) and nutrients (e.g., saturated fatty acids), significantly predicted inflammation. However, when HEI scores were used as a measure of diet quality, no clear association between diet quality and markers of immune function was observed across studies (Bujtor et al., 2021). It is therefore possible that this specific composite is less suitable for examining diet-induced inflammation compared to other dietary measures. Use of HEI-2015 scores in the present study may therefore have attenuated the association between diet quality and markers of inflammation.

Much of the existing research supporting an association between diet quality and inflammation has focused on CRP and/or IL-6 as individual markers of inflammation (Bujtor et al., 2021). While both CRP and IL-6 are widely used and are generally recognized as physiologically important markers of inflammation, analysis of single cytokines increases the risk of type I error (Fagundes et al., 2019; Knight et al., 2020). The inflammatory composite score used in the present study for both circulating and stimulated cytokine production included IL-6. However, because CRP is produced by the liver (Hurlimann et al., 1966), it was not possible to include CRP in the stimulated cytokine production composite. To ensure that both inflammatory composite scores included the same cytokines, CRP was not used in the circulating cytokine composite in the present study.

Comparably less research has examined the association between diet quality and *ex vivo* stimulated cytokine production. The majority of relevant research examines specific nutrients, rather than overall diet quality. Given the complex interactions between nutrients, interpreting the effects of individual nutrients can be challenging (Julibert et al., 2019; Kubena & McMurray, 1996). For example, omega-3 unsaturated fatty acids have been shown to suppress markers of immune function, including lymphocyte proliferation, cytokine production, and cytotoxicity, in both *in vivo* animal models and *ex vivo* human models; adding vitamin E attenuates this suppression (Calder & Newsholme, 1993; Kubena & McMurray, 1996). Importantly, however, much of the research investigating the effect of nutrients on *ex vivo* measures of immune function involves adding individual nutrients to the cell culture medium, rather than examining dietary intake of the nutrients (Calder & Newsholme, 1993; Kubena & McMurray, 1996; Mao et al., 2000). As such, whether or not these results translate to studies of diet quality is unclear.

To my knowledge, no research specifically addressing the impact of overall diet quality on *ex vivo* LPS stimulated cytokine production in humans has been published. However, one study has examined the effect of experimentally altering dietary fatty acid composition on *ex*

vivo LPS stimulated cytokine production (Koutsos et al., 2014) in a clinical trial of 88 normolipidemic participants who completed three 8-week isoenergetic diet periods: a low fat diet, a high saturated fat diet, and a high saturated fat + high DHA diet (Lockyer et al., 2011). The high saturated fat diet resulted in significantly higher TNF-α (i.e., a pro-inflammatory cytokine) production compared to the low-fat diet and baseline measures (Koutsos et al., 2014). The high saturated fat + high DHA diet resulted in higher TNF-α production compared to baseline. The low-fat diet resulted in significantly higher IL-10 (i.e., an anti-inflammatory cytokine) production compared to baseline and the high saturated fat + DHA diet (Koutsos et al., 2014). In sum, these results suggest that higher levels of saturated fat consumption may be pro-inflammatory, while a habitually low-fat diet may have anti-inflammatory properties. However, no significant change in IL-1β, IL-6, or IL-8 production was observed (Koutsos et al., 2014). Notably, IL-1β and IL-6 production were both included in the present stimulated cytokine production composite, which also yielded null results. As such, the impact of diet on immune function may not extend to these specific cytokines. Based on the results published to date, assessment of IL-10 and TNF-α production in response to *ex vivo* stimulation with LPS may be a promising avenue for examining associations between diet and immune function.

Markers of Immune Function were Not Significantly Associated with Depressive Symptoms

Circulating Cytokines and Depressive Symptoms

The present study found no association between circulating cytokines and depressive symptoms. While a substantial body of evidence suggests a relationship between inflammation and depression (Howren et al., 2009; Y. Liu et al., 2012; A. H. Miller & Raison, 2016; Patel, 2013; Yuan et al., 2019), the details of this relationship have yet to be fully delineated. Results have often been mixed, with some studies reporting no associations between circulating markers of inflammation and MDD (e.g., Einvik et al., 2012). It is possible that differences in statistical power may contribute to the different results observed. Individual studies with small

samples of approximately 100 participants, such as the present study and the study by Einvik and colleagues (2012) have produced null results, while larger meta-analyses of multiple studies typically report at least some significant findings (Howren et al., 2009; Y. Liu et al., 2012). It is worth noting that results also vary depending on the specific cytokines assessed. For example, a meta-analysis found that TNF-α and IL-6 were significantly associated with depression, while IL-1β, IL-4, IL-2, IL-8, IL-10, and IFN-y were not (Dowlati et al., 2010). Existing significant results could potentially be the result of type I error, as individual cytokine analyses are often used. Still, it is physiologically plausible that inflammation could result in symptoms of depression and the development of depressive disorders (e.g., Kiecolt-Glaser et al., 2015; A. H. Miller & Raison, 2016), and significant results have been observed consistently enough to suggest that there may be a true association.

Importantly, MDD is a heterogeneous disorder, with individual patients experiencing unique combinations of symptom types and symptom severity across different time scales (van Eeden et al., 2019). Inflammation may drive the development of specific depressive symptoms characterizing sickness behavior, such as fatigue and social withdrawal (Jokela et al., 2016; A. H. Miller & Raison, 2016). Prolonged inflammation may increase risk for depressive disorders by increasing these sickness behavior symptoms, and likely contributes to the high prevalence of MDD among medically ill individuals (Dantzer et al., 2006, 2008; Lotrich, 2015). Still, the association between inflammation and depression varies: not all people with inflammation develop a depressive disorder, and not all people with depressive disorders have elevated markers of inflammation. A meta-analysis of 30 studies found that depressed patients were more likely to have low grade inflammation (defined as CRP > 3mg/L) compared to control participants; however, only about 27% of participants with depression had low grade inflammation (Osimo et al., 2020). Thus, while people with depression are more likely to have low-grade inflammation compared to people without depression, the majority of people with depression do not have low-grade inflammation. One possible explanation is that inflammatory

cytokine-associated depression is a unique depression subtype, with distinct symptoms (i.e., greater experience of sickness behavior symptoms) and unique pro-inflammatory pathology that may not be involved in other depression subtypes (Lotrich, 2015). Additional research clarifying the physiological underpinnings of depressive symptoms and depression subtypes is needed to support the existence and clinical utility of such biological classification systems for depressive disorders (Beijers et al., 2019).

Stimulated Cytokine Production and Depressive Symptoms

The present study found no significant association between *ex vivo* stimulated cytokine production and depressive symptoms at either study visit. Few studies examining *ex vivo* stimulated cytokine production and major depressive disorder or depressive symptoms have been published, but existing evidence suggests that the two may be related (Knight et al., 2020; Majd et al., 2018). These published studies had a slightly larger sample than the present study, with 160 participants (Knight et al., 2020; Majd et al., 2018), and therefore had greater statistical power to detect an effect. Importantly, these studies reported no main effect between depressive symptoms and stimulated cytokine production, in line with the present findings. Instead, significant associations were seen in moderation analyses, which were not hypothesized in the present study. A significant interaction effect between depressive symptoms and gender on stimulated cytokine production has been reported (Majd et al., 2018). Similarly, a significant interaction effect between a marker of endotoxemia, gender, and depressive symptoms on stimulated cytokine production has been observed (Knight et al., 2020). In both published studies, the direction of the association between *ex vivo* stimulated cytokine production and depressive symptoms differed by sex (Knight et al., 2020; Majd et al., 2018). The present study did not specifically hypothesize any sex effects in the association between *ex vivo* cytokine production and depressive symptoms, largely out of concerns related to statistical power and the potential for unequal group sizes. The lack of significance observed in the present study could therefore potentially be a suppression effect resulting from differing

associations between *ex vivo* stimulated cytokine production and depressive symptoms across sexes. Future research aimed at examining sex differences in the association between *ex vivo* cytokine production and depression is warranted.

Markers of Immune Function were Not Significantly Associated with Metabolic Syndrome Symptom Severity

Circulating Cytokines and Metabolic Syndrome Symptom Severity

MetS is considered a chronic inflammatory disease (Fahed et al., 2022; Tamakoshi et al., 2003), and inflammation may drive MetS development even in children and adolescents (Wärnberg & Marcos, 2008). However, the association between circulating cytokines and MetS symptom severity was not significant in the present sample. One plausible explanation for this is that the study participants were all young (18 to 19 years old) and very few met full MetS criteria. Floor effects are commonly encountered in young and/or healthy individuals, whose circulating inflammatory markers often fall below the lower limit of detection (LLOD) (Kleiner et al., 2013; Zhou et al., 2010). In the present study, no participant was below the LLOD for circulating IFN-y or IL-6 at either visit. However, 8 participants fell below the LLOD for IL-1β at visit 1, and 32 participants were below the LLOD for IL-1β at visit 2. Please note that cytokine values below the LLOD were replaced with the LLOD for that cytokine as part of the data cleaning process. Past evidence suggests that IL-1β may be upregulated by seasonal allergies (Griffin et al., 2018), which generally are at their lowest in the winter (Schmidt, 2016). It is possible that this seasonal variability in cytokine levels may be partially responsible for the larger number of participants with undetectably low levels of IL-1β at visit 2 (in December) compared to visit 1 (in late August to early September). While measurable levels of all cytokines were observed in a majority of the present study participants, the lower levels of circulating cytokines in young people, and of IL-1β specifically in the present sample, may have reduced the ability to observe effects. Past research reporting a significant association between circulating markers of inflammation and MetS symptoms in young people has often focused on

CRP (Wärnberg & Marcos, 2008), possibly in attempt to avoid the known floor effects of other cytokines in young people (Kleiner et al., 2013; Zhou et al., 2010). It is also possible that differences in sample size, and therefore statistical power, may contribute to the inconsistent findings observed. However, a meta-analysis has reported no correlation between sample size and effect size across studies of inflammation and depression (Dowlati et al., 2010). Additionally, past research has found elevated circulating CRP only in youths with three of more symptoms of MetS (Wärnberg & Marcos, 2008). In the present study, only one participant had at least three symptoms of MetS at visit 1, increasing to three participants at visit 2. Thus, it is possible that individuals in the present sample did not have severe enough MetS symptoms for the association between MetS and circulating markers of inflammation to be observed.

Stimulated Cytokines and Metabolic Syndrome Symptom Severity

Ex vivo LPS-stimulated cytokine production was not associated with MetS symptom severity in the present study at either visit. It is theoretically plausible that *ex vivo* LPS-stimulated cytokine production could reflect inflammation related disease risk, including risk of MetS. Lipopolysaccharide (LPS) promotes inflammation by binding to and activating TLR4 (Chow et al., 1999; Schletter et al., 1995), and past research suggests that TLR4 expression contributes to the development of MetS (Jialal et al., 2021; Jialal et al., 2012). The TLR4 / NF-κB pathway also appears to be a mechanism in diet-induced inflammation (Kim et al., 2014; Nobs et al., 2020); measurement of *ex vivo* LPS-stimulated inflammation was included in the present study in part because it may be a valid proxy measure of the pro-inflammatory process linking poor diet quality to the development of MetS. While one aim of the present study was to examine the potential for *ex vivo* cytokine production as a measure of disease risk in pre-clinical samples, it is possible that the lack of results observed may be due to the young age and low degree of MetS symptom severity in the present sample. Supporting this, a published cross-sectional study reported significant associations between essential hypertension (i.e., high blood pressure), a MetS symptom, and *ex vivo* LPS stimulated IL-1 and IL-6 production in a sample of

63 participants (Peeters et al., 2001), suggesting that this measure may have potential as an indicator of cardiovascular health. This study had a smaller sample than the present study, and therefore had even lower power to detect an effect. However, the participants were older than the present sample on average, with a mean age of approximately 47 years (Peeters et al., 2001). It is therefore plausible that the association between *ex vivo* stimulated cytokine production and cardiometabolic health may only become apparent as individuals age and develop more advanced markers of CVD risk, such as essential hypertension.

To my knowledge, only one publication has directly tested the association between *ex vivo* LPS stimulated cytokine production and MetS in humans. Mærkedahl and colleagues (2018) found that MetS and its components were not significantly related to *ex vivo* LPS stimulated cytokine production after 24 hours of incubation, including production of IL-1β, IL-8, IL-6 and TNF-α. Thus, the present study results are in line with existing literature. In the published study, differences in *ex vivo* stimulated cytokine production were examined in a sample of adults who were overweight and met at least one MetS criterion (Mærkedahl et al., 2018). In the present study, the majority of participants had relatively good cardiometabolic health, with few meeting more than one criterion at each time point. Future research should consider comparing *ex vivo* stimulated cytokine production in individuals with and without MetS, to determine whether the measure effectively differentiates those who do and do not meet full MetS criteria.

Circulating Cytokines, Stimulated Cytokines, and Depressive Symptoms did Not Change Significantly across the Semester

Despite the observed changes in MetS symptom severity and diet quality, no significant change was observed in circulating cytokines, stimulated cytokine production, or depressive symptoms across the semester. There are several plausible reasons for the lack of change. First, the time points during which data were collected could have impacted the present findings. Visit 1 occurred within the first month of the start of the semester, capturing a highly stressful

transitional period (Conley et al., 2014; Dyson & Renk, 2006; Kroshus et al., 2021). Visit 2 occurred near the end of the semester, in the two weeks of classes before the start of finals week. While collecting data during finals week was deliberately avoided to reduce the impact of exam-related stress, it is still plausible that students were experiencing high stress levels in the weeks before finals, when they may have been attempting to finish remaining class projects and prepare for the upcoming final exam period. This may have been more impactful in the present study design, because participants were incoming first-year students undergoing their first experience with college-level final exams. Thus, stress levels may have been higher than normal at both time points. Because stress influences circulating cytokine levels (G. E. Miller et al., 2002; Rohleder, 2014, 2019) and depressive symptoms (Hammen, 2005; Raison & Miller, 2001; Van Praag, 2004), this may have confounded the present results. *Ex vivo* stimulated cytokine production may have a similar response pattern as levels of cortisol after exposure to stress, and these measures may capture comparable information about human stress responses (Davis et al., 2020). As such, it is possible that the students' high stress levels at both study visits may have contributed to the lack of change in *ex vivo* stimulated cytokine production. Past research has also found that depressive symptoms are fairly stable within-person across time spans longer than the 4 months of the present study, including periods of 10 months (Minor et al., 2005) and 2 years (Lamers et al., 2012). Additional longitudinal research with more frequent data collection points would help determine whether or not markers of immune function and depressive symptoms fluctuate across the course of the semester.

Circulating Cytokines and Stimulated Cytokines were Significantly Correlated

While no hypotheses were made about the association between circulating cytokines and stimulated cytokine production, the two measures were significantly correlated in the present sample at both visit 1 ($r = .415$, $p < .001$) and at visit 2 ($r = .251$, $p = .014$). This contrasts with some past research reporting no correlation between circulating cytokines and *ex vivo* LPS stimulated cytokine production (Davis et al., 2020; Mærkedahl et al., 2018; Majd et al.,

2018). The young age of our study participants may play a role in the unexpected correlation, as immune dysregulation develops across the lifespan. The lifelong process by which elevated circulating cytokines contribute to overstimulation of the immune system and immune dysregulation has been called inflamm-aging (Franceschi et al., 2000; Weiskopf et al., 2009) or immune senescence (Ben-Yehuda & Weksler, 1992; Ponnappan & Ponnappan, 2011). Inflamm-aging involves age-related increases in number of NK cells and circulating levels of inflammatory cytokines, including IL-6, IL-1β, and TNF-α (Ponnappan & Ponnappan, 2011; Weiskopf et al., 2009). However, NK cell cytotoxicity, immune cell proliferation, phagocytic activity, and the ability to activate T-cells all decline with increasing age (Ponnappan & Ponnappan, 2011; Weiskopf et al., 2009). Age-related immune dysregulation may therefore involve the development of immune tolerance, wherein cells become less responsive to the cytokine signals of the immune system, (J. Wu et al., 2014). In turn, immune tolerance may contribute to the interesting combination of reduced immune system efficacy (leading to greater risk of infection) and elevated circulating cytokine levels that is often observed in the elderly (Ben-Yehuda & Weksler, 1992; Ponnappan & Ponnappan, 2011; J. Wu et al., 2014). Immune senescence may be a factor in the lack of correlation observed between circulating cytokines and stimulated cytokine production in past research, which has typically included participants up to 65 or 70 years of age (Davis et al., 2020; Knight et al., 2020; Mærkedahl et al., 2018; Majd et al., 2018). In the current and younger sample, the correlation between these markers of immune function may indicate a broadly more functional immune system that is capable of responding to pathogen threats, and then suppressing that response, in an effective manner without resulting in chronically elevated circulating cytokines.

Stress and coping skills are also plausible mechanisms explaining the observed association between circulating cytokines and *ex vivo* stimulated cytokine production in the present sample. *Ex vivo* stimulated cytokine production has a similar response pattern as post-stress cortisol levels, such that these measures may capture similar information about human

stress responses (Davis et al., 2020). The transition into college and preparing for your first college-level final exams are highly stressful time periods for many incoming first-year students. However, much of the existing knowledge about the association between circulating cytokine and *ex vivo* stimulated cytokine production has been derived from samples including older adults (Davis et al., 2020; Knight et al., 2020; Mærkedahl et al., 2018; Majd et al., 2018). While the association between perceived stress levels and age depends upon how stress is operationally defined, older adults may have better coping skills than young adults, enabling more effective stress management (Aldwin, 2011). Past research suggests that coping skills may influence cortisol reactivity (Dhabhar, 2014; Sladek et al., 2016). Greater levels of perceived stress have been shown to elicit elevated cortisol levels in individuals with low levels of engagement coping and low belief in their own ability to cope with the stress, while participants with greater coping skills do not exhibit the same increase in cortisol in response to increases in perceived stress (Sladek et al., 2016). Because coping skills influence cortisol stress responses (Sladek et al., 2016), and *ex vivo* stimulated cytokine production may be analogous to cortisol stress responses (Davis et al., 2020), coping skills may also influence *ex vivo* stimulated cytokine production. Thus, it is possible that differences in coping skills between older and younger adults may contribute to the inconsistent results observed across study samples. Additional research could help determine whether coping skills influence *ex vivo* stimulated cytokine production. Research investigating whether *ex vivo* stimulated cytokine production and the association between circulating and stimulated inflammatory markers change across the lifespan is also warranted.

The Role of Sex as a Covariate Differed across Study Visits

Sex was significantly associated with diet quality and depressive symptoms at visit 2, but not visit 1. Conversely, sex was significantly associated with stimulated cytokines at visit 1, but not at visit 2. There are several plausible explanations for these apparent discrepancies. First, past research has provided evidence for sex differences in the experience of transitioning to

college (Alfeld-Liro & Sigelman, 1998; Beaudry et al., 2019; Calaguas, 2011; Fisher & Hood, 1988). For example, males have been found to have a higher degree of adjustment difficulty in the first year of college compared to female students (Calaguas, 2011). When measures were taken the summer before starting college, no sex differences in self-concept were observed; however, males experienced improvement in self-concept across the transition into college, such that sex differences were significant at the end of the first semester (Alfeld-Liro & Sigelman, 1998). Interestingly, by the middle of the second year in college, female students had improved in self-concept enough that there were no longer significant sex differences (Alfeld-Liro & Sigelman, 1998). Thus, it appears that males and females may experience the psychological effects of transitioning into college across different time scales. Seasonality may also be a factor in the present pattern of results, as Seasonal Affective Disorder, a depressive disorder characterized by increased depressive symptoms in winter months, may be more prevalent in females than in males (T. M. C. Lee & Chan, 1998; Lucht & Kasper, 1999; Thalén et al., 1995). Future research examining changes in mental and physical health across the college years should consider investigating sex differences as an *a priori* outcome of interest. Including multiple measurement occasions across semesters in college could also help clarify whether sex differences observed at one time point persist across time.

Limitations

One potential limitation of the proposed study is the examination of changes across the first semester of college, specifically, rather than the first academic year or total time in college. However, while changes in biobehavioral health are likely to continue across time in college, the goal of the proposed study was to more closely examine the transition into college, a period of rapid change in environment and lifestyle (Bowman et al., 2019; Butler et al., 2004). Inclusion of students in their second semester and beyond would not capture the intended transitionary period. In addition, past research suggests that significant changes in body weight, body fat percentage, and depressive symptoms occur within the first semester of college (Barker et al.,

2018; Ludy et al., 2018; Reisbig et al., 2012; Wengreen & Moncur, 2009), and that changes across the second semester are relatively small by comparison (Barker et al., 2018; Reisbig et al., 2012). Consequently, further research regarding the extent and causes of declining health across the first semester is warranted.

A related limitation is the lack of a clear definition for the 'transition to college'. It is unclear precisely how long this transition period is, or whether there are any valid markers of a person successfully completing the transition process. The present study defined the transition period as the first semester of college. Measures were taken at the beginning and end of the first semester, acknowledging that the study group could not recruit students prior to their arrival on campus. As such, limited information is available regarding the health and health behaviors of the participants prior to initiating college. If the transition to college is defined as beginning before the start of the first semester, then the present study does not capture the full transition period. However, existing studies have captured the transition to college at different time points and across different time scales. One cross-sectional study assessed adjustment difficulties during the 6th week of the first semester of college (Fisher & Hood, 1988). Another cross-sectional study took measures during the first semester, noting that difficulty adjusting to college life across the first semester is a primary reason that many students drop out before beginning the second semester (Calaguas, 2011). Repeated measures studies have taken baseline measures in the summer between ending high school and beginning college, with follow up measures at the end of the first semester (Alfeld-Liro & Sigelman, 1998), or across the first year (Conley et al., 2014; Kroshus et al., 2021). Other repeated measures studies have taken measures at the beginning and end of the first semester (D. A. Anderson et al., 2003), in line with the present study design, or at the beginning and end of the first year (Beaudry et al., 2019). Given that each new semester brings a new set of classes, each semester could be considered a new transitionary period. From a lifespan perspective, college itself is a relatively short time frame, taking about 4 years out of the 77 years that Americans can expect to live

(Murphy et al., 2021); all 4 years could therefore be considered a transitionary period between finishing high school and starting a career. Capturing the beginning and end of the first semester in college appears to be a plausible method for understanding aspects of the transition to college. However, further research examining varying time scales would help determine whether there are critical periods for change across the transition into and years spent in college.

Another possible limitation stems from challenges surrounding memory-based 24-hour diet recall systems. Past research suggests that participants may misrepresent their dietary intake due to memory errors and/or social desirability bias (Archer et al., 2015). However, all currently available measures of diet quality are prone to these issues (Ortega et al., 2015; Subar et al., 2015), and existing evidence suggests that multiple pass 24-hour diet recall systems, including ASA24, offer improved diet quality metrics compared to other commonly used tools, such as food frequency questionnaires and food diaries (Burrows et al., 2010; Kipnis et al., 2003; Subar et al., 2015). In addition, because individuals tend to eat differently on different days, a single 24-hour diet recall is unlikely to adequately describe dietary patterns. Past research suggests that three separate 24-hour diet recalls is the optimum number to accurately assess diet quality, ideally with two recalls taking place on weekdays, and one over the weekend (Burrows et al., 2010; Ma et al., 2009). Thus, this measure of diet quality is empirically supported, despite its potential limitations. Importantly, though, diet quality may be less consistent in college students compared to other groups: fluctuations in finances, food availability, and social pressures may result in inconsistent dietary habits in college students, and perhaps young adults more broadly (S. Collins et al., 2022; Ganasegeran et al., 2012). Consequently, single summary measures of overall diet quality may be more biased and less valid in these populations. While the present study attempted to improve the validity of diet quality measures and attenuate the effect of day-to-day variability in diet by assessing diet

quality on three days at each time point, results may still be limited by the particularly high variability of dietary habits among college students.

This study is further limited by lack of information regarding where students consumed each meal. The majority of participants had campus meal plans, and therefore were likely to consume many if not most of their meals in campus dining facilities. However, no data were collected specifying whether meals were consumed on-campus or off-campus. Past research has found that students who eat in campus dining facilities more often may have lower quality diets compared to those who eat off campus more often (Pelletier & Laska, 2013). Unfortunately, the present study is not able to assess whether this pattern is also true at Penn State.

Finally, this study may have limited generalizability, for several reasons. First, we were required to include weighing < 110 pounds as an exclusion criterion due to our collection of blood samples. This criterion matches the 110-pound minimum weight required by the American Red Cross for donating blood, which is used because individuals weighing less than 110 pounds may not have sufficient blood volume to safely donate a pint of blood. While we did not collect a large blood sample from our participants, the Institutional Review Board required us to follow the American Red Cross weight guidelines to ensure participant safety. Using a low BMI as an inclusion criterion instead of a weight requirement would have been preferable here, as the use of the 110-pound criteria more substantially impacts the ability of females to participate compared to males. The present study had proportionately more female than male participants; still, the use of a minimum weight criterion reduced the ability of females of a shorter height to participate. As such, the females in the present sample may not be an accurate representation of the overall female student population. Additionally, this study was conducted during the COVID-19 pandemic, during the first in-person semester after several semesters of completely or partially remote learning in both colleges and high schools. Students may have felt additional stress and anxiety about moving into a dormitory with other incoming students and returning to

in-person classes due to the possibility of getting infected with COVID-19. Conversely, some students may have experienced some psychological benefit of having in-person social support and a return to some semblance of normal routines after a period of prolonged isolation and uncertainty. It is not possible to determine the degree to which this highly unusual situation may have impacted the mental and physical well-being of the current sample, as compared to the effect of transitioning to college. Thus, study results may be confounded by COVID-19 related factors, and the generalizability of these results to other incoming first-year cohorts may be limited.

Future Directions

First, there are several interesting analyses that could be done using the data collected in the present research project. For example, measures of childhood socioeconomic status were collected. Due to the influence of SES on both diet quality (Darmon & Drewnowski, 2008, 2015), and cardiometabolic health (Agardh et al., 2011; de Mestral & Stringhini, 2017; Zilioli et al., 2022), it would be very interesting to explore these data. Provided that there is sufficient variability in the SES of the sample, an analysis exploring whether childhood SES predicts the diet quality and MetS symptom severity would be informative. Additionally, alcohol use was also assessed at both time points using the Daily Drinking Questionnaire (R. L. Collins et al., 1985), and initial comparisons suggest that alcohol use significantly increased across the course of the semester. The ASA-24 diet recall measure also collects information about alcohol consumption, and this information is included in the total caloric intake values presented. However, alcohol is not part of the calculations for the HEI-2015 scores (Krebs-Smith et al., 2018), and as such was not reflected in the present analyses. Further, past research has found associations between alcohol use and stress (Peltier et al., 2019), MDD (Boden & Fergusson, 2011), markers of inflammation (Bishehsari et al., 2013; Kazmi et al., 2022), and MetS (Stoutenberg et al., 2013). Analyses testing whether alcohol use in the present sample of first-year college students is

associated with these factors both concurrently at each time point and across the course of the semester, could prove informative.

This research project also inspires new questions that should be investigated in future studies. For example, our incidental finding that measures of circulating and stimulated cytokines are correlated in the present sample, despite several publications finding that these measures are not correlated in older adults (Davis et al., 2020; Mærkedahl et al., 2018; Majd et al., 2018), is very interesting. Future research investigating whether the association between these two measures changes across the lifespan, perhaps as part of the 'inflamm-aging' process, could provide a great deal of insight into age-related changes in immune function. Cross-sectional designs recruiting samples across different age ranges could be beneficial here. However, longitudinal designs following the same individuals across time would be most informative.

The present finding of no association between markers of inflammation and depressive symptoms is perhaps unsurprising, given that only 16.4% of the present sample (18 participants) met clinical criteria for a major depressive episode, and only about 27% of people with MDD exhibit elevated markers of inflammation (Osimo et al., 2020). However, it is still plausible that some cases of MDD among young people could involve or even be driven by inflammation. Additional research targeting young patients with MDD would help delineate whether or not the proportion of patients with MDD and elevated markers of inflammation is similar among younger populations and older adult populations. Further, research more closely examining patients with depression, considering their subjective symptoms as well as markers of inflammation, could help elucidate whether inflammation-induced depression is a unique subtype of depression. Longitudinal studies tracking symptom clusters and biomarkers across time would be particularly informative. Research aimed at delineating the causes and symptoms of MDD and other subtypes of depression could help develop more targeted depression

treatments, and hopefully improve mental and physical health outcomes among people with depression.

Another important future direction relates to the issue of campus food policy. The present study found that students' diet quality was low at both time points, and that both diet quality and MetS symptom severity worsened across the semester. Because the students are generally required to live on campus and to have a campus meal plan, Penn State could play a role in increasing the number of students who meet dietary guidelines to protect their cardiometabolic health. However, implementing such policies effectively would require additional research investigating where exactly the current policies fall short, and what types of changes could feasibly be made. For example, students failed to meet recommendations for whole grain consumption, and I have posited replacing refined grain products with whole grain products to improve adherence to the dietary guideline for whole grains. However, doing this would require research into what refined grain products are being provided in campus dining halls, and of these, which could reasonably be replaced. Further, research examining whether the students actually enjoy and would be willing to eat the healthful food options being made available is warranted: providing additional healthy food options will only result in food waste if the students are not willing to eat them. However, past research indicates that students would prefer to eat healthier options, but report that the lack of available healthy options makes this very difficult (Roy et al., 2019). As such, providing sufficient healthy options could help 'move the needle' on student diet quality. Some interesting research suggests that simple changes, such as labelling healthy foods in a more enticing way, could improve the quality of foods selected (Turnwald et al., 2017; Turnwald & Crum, 2019); for example, students were more likely to select a vegetable dish labeled as "crispy veggie straws with decadent miso dip" compared to the same dish labeled as "fiber-packed vegetables with nutritious miso sauce" (Turnwald & Crum, 2019). Other potentially beneficial strategies include placing the healthy options in more visible and prominent locations, and clearly labelling all food options with

relevant nutrition information (Bassett et al., 2008; Cameron et al., 2016; Shaw et al., 2020; Vogel et al., 2021). Penn State has an interesting advantage here, as there are several dining halls on campus. Research could be conducted to test the efficacy of such changes to placement and labelling of food products by implementing the change in half of the dining halls, then comparing the meal quality of students eating in the experimental and control dining halls. Because students with a meal plan are able to access all of the dining halls, study participants would need to be restricted to eating in a particular dining hall (or set of dining halls). Such research would help clarify which policies would be most effective for the student body here.

Conclusions

The present study found significant associations between diet quality and MetS symptom severity in a sample of first-semester college students. This finding adds to a growing body of literature highlighting the importance of maintaining a high-quality diet for the protection of cardiometabolic health. Of particular importance, all participants were young adults aged 18 to 19 years. Given that MetS is a chronic inflammatory disease that contributes to the development of CVD and T2D across time (Fahed et al., 2022; Mottillo et al., 2010; Rao et al., 2014), this finding underscores the need for developing primary prevention programs aimed at lifestyle-based cardiometabolic disease prevention in younger individuals. The entry into college may be an ideal time to initiate these programs, particularly dietary interventions, as this period often represents the transition to independence and may be the first time that these young adults need to independently provide their own meals (e.g., Beaudry et al., 2019).

Diet quality was found to decline across the semester, while MetS symptom severity increased. While the decline in diet quality did not predict MetS symptom severity at visit 2, these findings suggest that students developed worse dietary habits and worse cardiometabolic health within just the first semester of entering college. All participants were current first-year students at Penn State, and the vast majority of participants resided in on-campus housing and had a campus meal plan; consequently, these findings could help inform university policy

choices. Policies aimed at providing healthier food options in dining halls and encouraging healthier dietary choices through course materials or public service announcements on campus could enable students to consume a higher quality diet. While there are likely healthy options available in campus dining halls, students do not appear to be making healthy dietary choices based on the present observations. Ensuring that the healthy food options are displayed prominently and labelled clearly could encourage students to make better dietary choices. Enabling students to meet dietary guidelines could yield substantial reductions in their long-term cardiometabolic disease risk.

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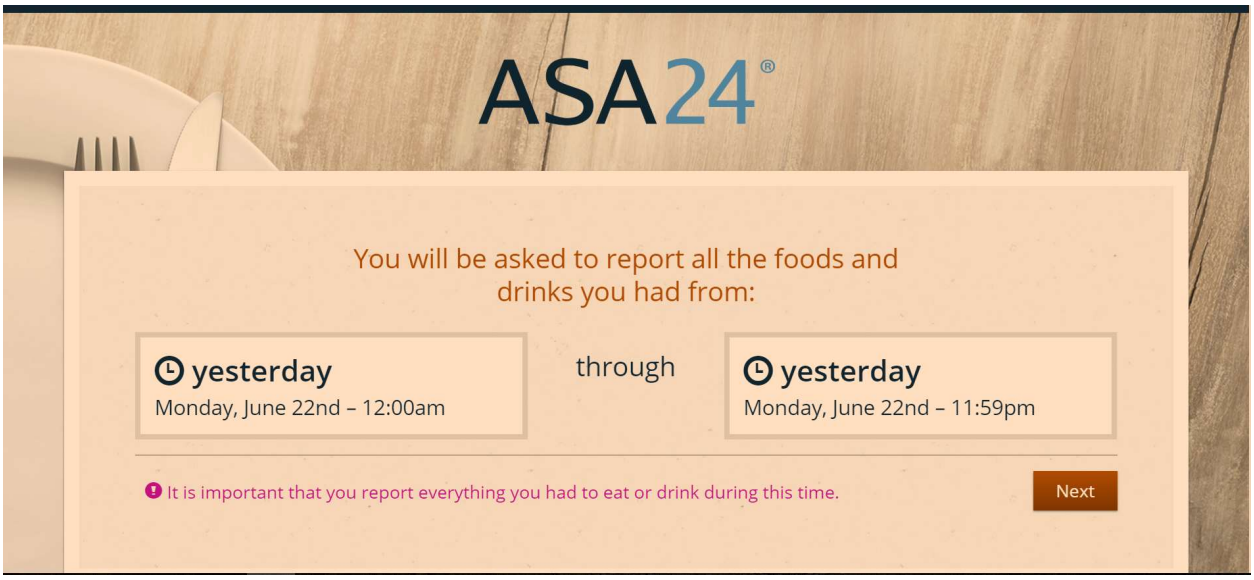
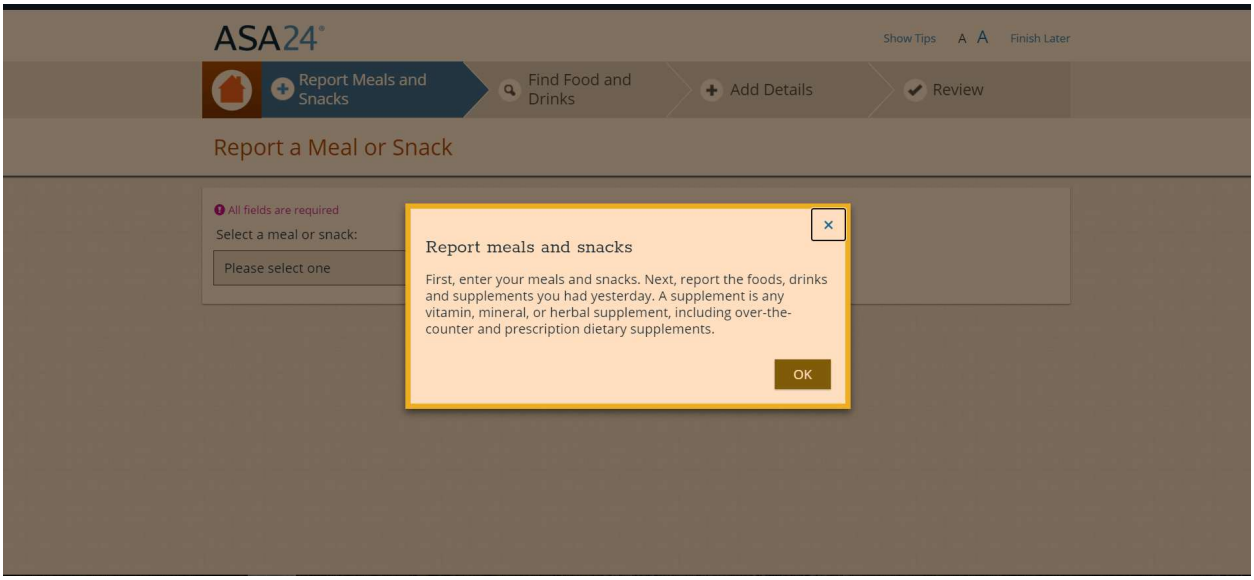
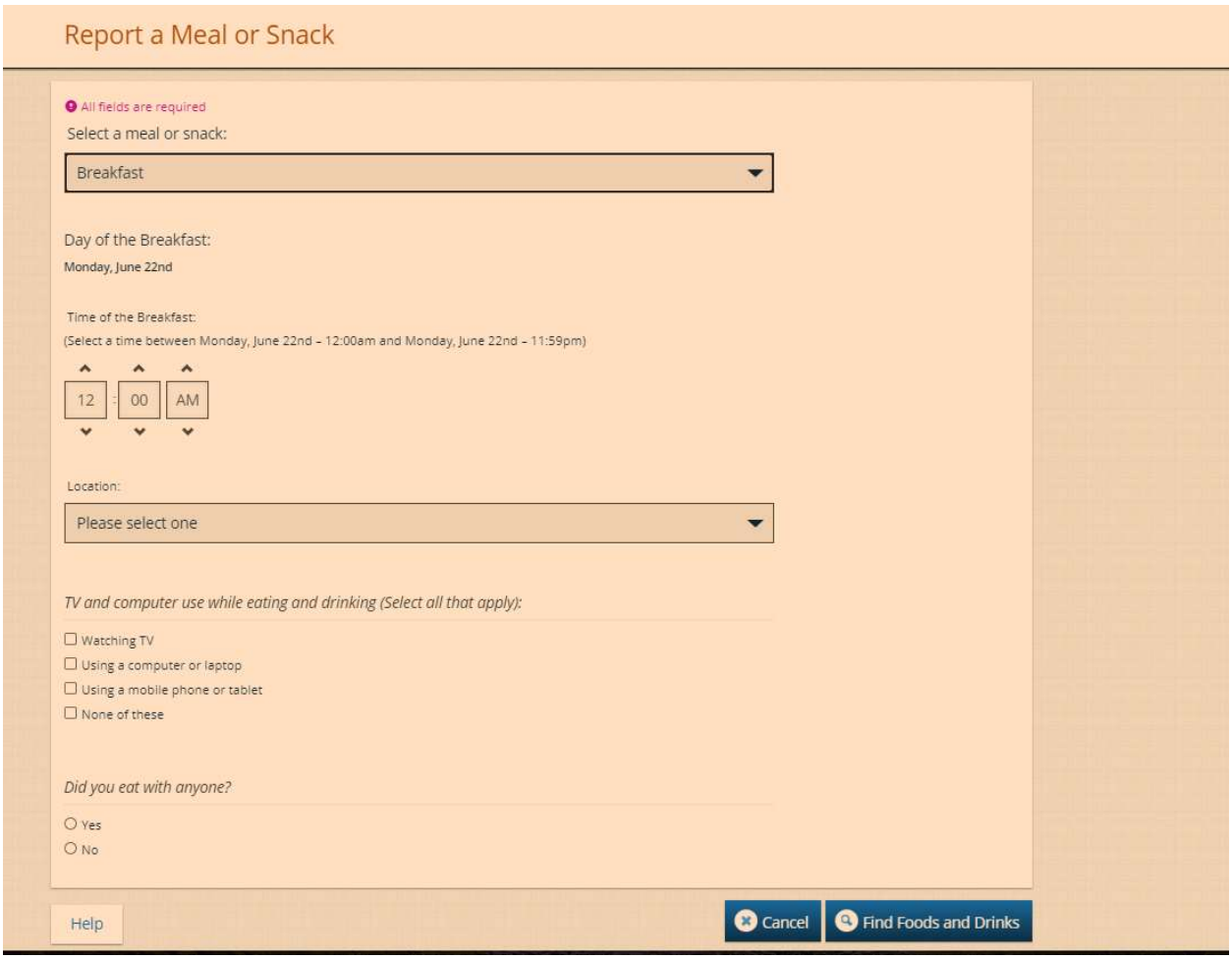
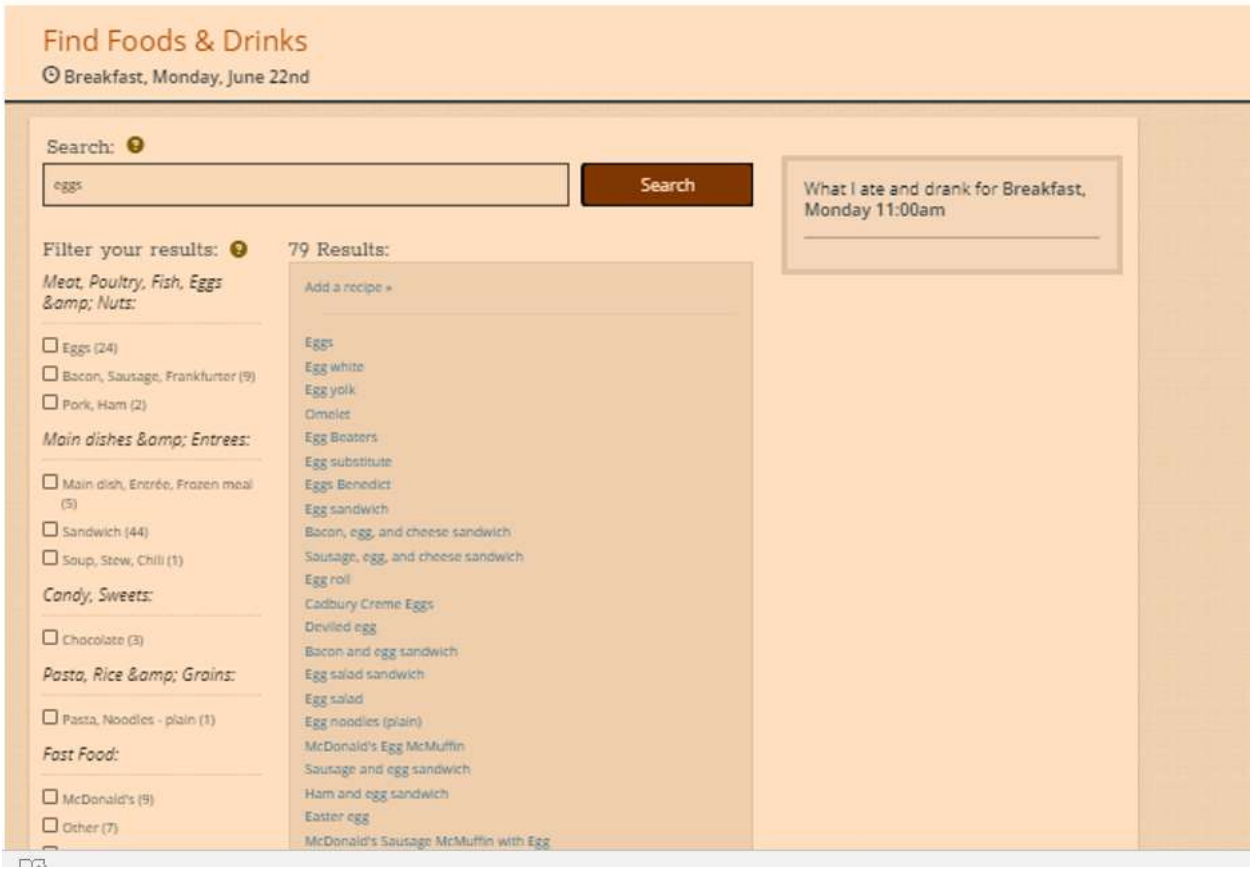
APPENDICES

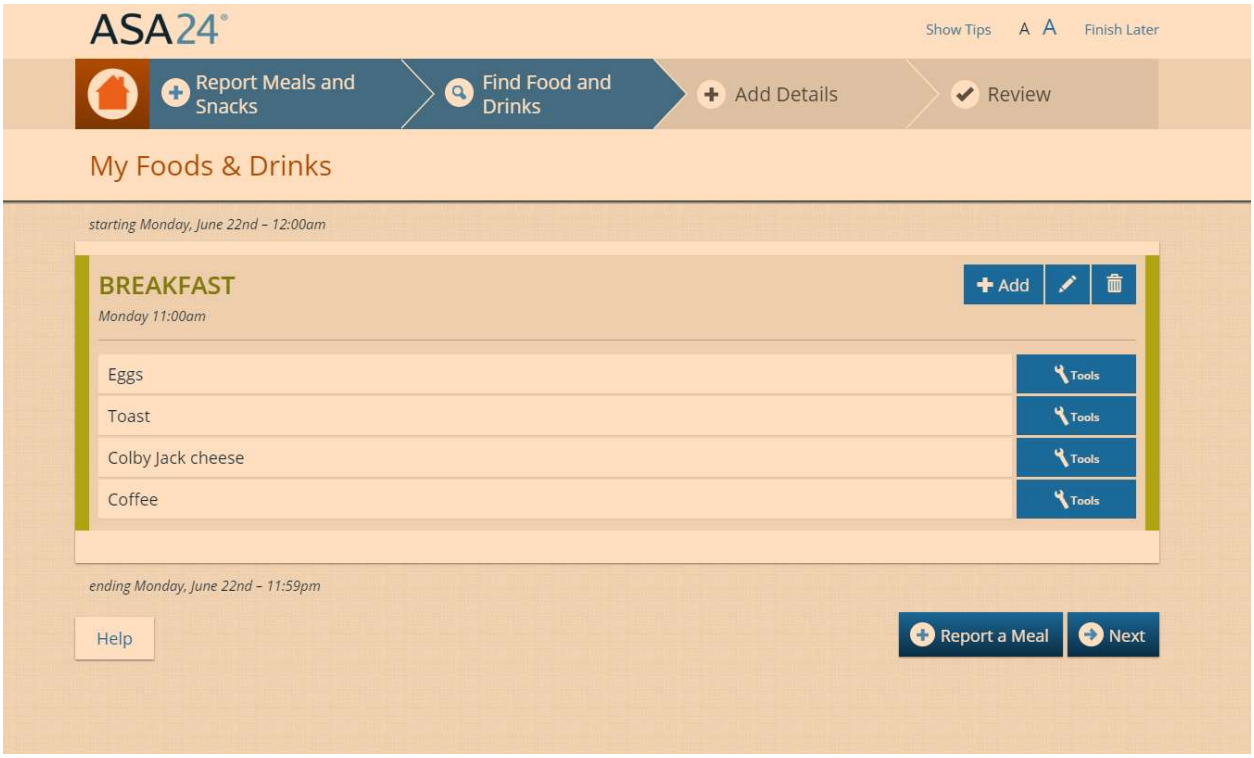
Appendix A: Screenshots from the Automated Self-Administered 24-hour (ASA24) Diet Recall System






Report a Meal or Snack
All fields are required
Select a meal or snack:
Breakfast
Day of the Breakfast:
Monday, June 22nd
Time of the Breakfast:
(Select a time between Monday, June 22nd - 12:00am and Monday, June 22nd - 11:59pm)
12
00
AM
Location:
Please select one
TV and computer use while eating and drinking (Select all that apply):
Watching TV
Using a computer or laptop
Using a mobile phone or tablet
None of these
Did you eat with anyone?
Yes
No
Help
Cancel
Find Foods and Drinks


Find Foods & Drinks
Breakfast, Monday, June 22nd
Search:
eggs
Search
What I ate and drank for Breakfast, Monday 11:00am
Filter your results:
79 Results:
Meat, Poultry, Fish, Eggs & Nuts:
Eggs (24)
Bacon, Sausage, Frankfurter (9)
Pork, Ham (2)
Main dishes & Entrees:
Main dish, Entrée, Frozen meal (5)
Sandwich (44)
Soup, Stew, Chili (1)
Candy, Sweets:
Chocolate (3)
Pasta, Rice & Grains:
Pasta, Noodles - plain (1)
Fast Food:
McDonald's (9)
Other (7)
Add a recipe »
Eggs
Egg white
Egg yolk
Omelet
Egg Beaters
Egg substitute
Eggs Benedict
Egg sandwich
Bacon, egg, and cheese sandwich
Sausage, egg, and cheese sandwich
Egg roll
Cadbury Creme Eggs
Deviled egg
Bacon and egg sandwich
Egg salad sandwich
Egg salad
Egg noodles (plain)
McDonald's Egg McMuffin
Sausage and egg sandwich
Ham and egg sandwich
Easter egg
McDonald's Sausage McMuffin with Egg


ASA24
Show Tips
A A
Finish Later
Report Meals and Snacks
Find Food and Drinks
Add Details
Review
My Foods & Drinks
starting Monday, June 22nd – 12:00am
BREAKFAST
Monday 11:00am
Add
Eggs
Toast
Colby Jack cheese
Coffee
Tools
ending Monday, June 22nd – 11:59pm
Help
Report a Meal
Next

Appendix B: The Beck Depression Inventory - 2nd Edition (BDI-II)

The Beck Depression Inventory - 2nd Edition

Please read each group of statements carefully, and then pick out the one statement in each group that best describes the way you have been feeling during the past 2 weeks, including today.

1. Sadness
   - 0 I do not feel sad.
   - 1 I feel sad.
   - 2 I am sad all the time.
   - 3 I am so sad or unhappy that I can't stand it.
2. Pessimism
   - 0 I am not discouraged about my future.
   - 1 I feel more discouraged about my future than I used to be.
   - 2 I do not expect things to work out for me.
   - 3 I feel my future is hopeless and will only get worse.
3. Past Failure
   - 0 I do not feel like a failure.
   - 1 I feel I have failed more than I should have.
   - 2 As I look back, I see a lot of failures.
   - 3 I feel I am a total failure as a person.
4. Loss of Pleasure
   - 0 I get as much pleasure as I ever did from the things I enjoy.
   - 1 I don't enjoy things as much as I used to.
   - 2 I get very little pleasure from the things I used to enjoy.
   - 3 I can’t get any pleasure from the things I used to enjoy.
5. Guilty Feelings
   - 0 I don't feel particularly guilty.
   - 1 I feel guilty over many things I have done or should have done.
   - 2 I feel quite guilty most of the time.
   - 3 I feel guilty all of the time.

6. Punishment Feelings

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. Self-Dislike

0 I feel the same about myself as ever.

1 I have lost confidence in myself.

2 I am disappointed in myself

3 I dislike myself.

8. Self-Criticalness

0 I don't criticize or blame myself more than usual.

1 I am more critical of myself than I used to be.

2 I criticize myself for all of my faults.

3 I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes

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. Crying

0 I don't cry any more than I used to.

1 I cry more now than I used to.

2 I cry over every little thing.

3 I feel like crying, but I can’t.

11. Agitation

0 I am no more restless or wound up than usual.

1 I feel more restless or wound up than usual.

2 I am so restless or agitated that it’s hard to stay still.

3 I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0 I have not lost interest in other people or activities

1 I am less interested in other people or things than before.

2 I have lost most of my interest in other people or things.

3 It's hard to get interested in anything.

13. Indecisiveness

0 I make decisions about as well as ever.

1 I find it more difficult to make decisions than usual.

2 I have greater difficulty in making decisions more than I used to.

3 I have trouble making any decisions.

14. Worthlessness

0 I do not feel I am worthless.

1 I don't consider myself as worthwhile and useful as I used to.

2 I feel more worthless as compared to other people.

3 I feel utterly worthless.

15. Loss of Energy

0 I have as much energy as ever.

1 I have less energy than I used to have.

2 I don't have enough energy to do very much.

3 I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0 I have not experienced any change in my sleeping pattern.

1 I sleep somewhat more than usual.

2 I sleep somewhat less than usual.

3 I sleep a lot more than usual.

4 I sleep a lot less than usual.

5 I sleep most of the day.

6 I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0 I am no more irritable than usual.

1 I am more irritable than usual.

2 I am much more irritable than usual.

3 I am irritable all the time.

18. Changes in Appetite

0 I have not experienced any change in my appetite.

1 My appetite is somewhat less than usual.

2 My appetite is somewhat more than usual.

3 My appetite is much less than before.

4 My appetite is much greater than usual.

5 I have no appetite at all.

6 I crave food all the time.

19. Concentration Difficulty

0 I can concentrate a well as ever.

1 I can't concentrate as well as usual.

2 It's hard to keep my mind on anything for very long.

3 I find I can't concentrate on anything.

20. Tiredness or Fatigue

0 I am no more tired or fatigued than usual.

1 I get more tired or fatigued more easily than usual.

2 I am too tired or fatigued to do a lot of the things I used to do.

3 I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

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 am much less interested in sex now.

3 I have lost interest in sex completely.

Appendix C: Godin-Shephard Physical Activity Scale

THE GODIN-SHEPHARD LEISURE-TIME PHYSICAL ACTIVITY QUESTIONNAIRE

Figure 1: THE GODIN AND SHEPHARD LEISURE-TIME PHYSICAL ACTIVITY QUESTIONNAIRE

During a typical **7-day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number).

	Times per week
STRENOUS EXERCISE **(HEART BEATS RAPIDLY)** (e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)	_____
MODERATE EXERCISE **(NOT EXHAUSTING)** (e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)	_____
MILD EXERCISE **(MINIMAL EFFORT)** (e.g., yoga, archery, fishing from river bank, bowling, horseshoeing, golf without using a cart, snow-mobiling, easy walking)	_____

Appendix D: Pittsburgh Sleep Quality Index (PSQI)

PITTSBURGH SLEEP QUALITY INDEX (PSQI)

1. During the past month, when have you usually gone to bed at night?

_____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

_____

3. During the past month, when have you usually gotten up in the morning?

_____

4A. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spend in bed.)

_____

4B. How many hours were you in bed?

_____

INSTRUCTIONS: For each of the remaining questions, check the one best response. Please answer all questions.

---

5. During the past month, how often have you had trouble sleeping because you…

	Never	Less than once a week	1-2 times a week	3+ times a week
(a) …cannot get to sleep within 30 minutes	◯	◯	◯	◯
(b) …wake up in the middle of the night or early morning	◯	◯	◯	◯
(c) …have to get up to use the bathroom	◯	◯	◯	◯
(d) …cannot breathe comfortably	◯	◯	◯	◯
(e) …cough or snore loudly	◯	◯	◯	◯
(f) …feel too cold	◯	◯	◯	◯
(g) …feel too hot	◯	◯	◯	◯
(h) …had bad dreams	◯	◯	◯	◯
(i) …have pain	◯	◯	◯	◯

(j) Other reason(s), please describe

_____

How often during the past month have you had trouble sleeping because of this?	○	○	○	○

	Not during the past month	Less than once a week	Once or twice a week	3 or more times a week
6. During the past month, how often have you taken medicine (prescribed or "over the counter") to help you sleep?	○	○	○	○
7. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?	○	○	○	○

	No problem at all	Only a very slight problem	Once or twice a week	3 or more times a week
8. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?	○	○	○	○

	Very good	Fairly good	Fairly bad	Very bad
9. During the past month, how would you rate your sleep quality overall?	○	○	○	○

Appendix E: Perceived Stress Scale (PSS)

Perceived Stress Scale (10 items)

INSTRUCTIONS:

The questions in this scale ask you about your feelings and thoughts during the last month. In each case, please indicate with a check how often you felt or thought a certain way.

1. In the last month, how often have you been upset because of something that happened unexpectedly?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

2. In the last month, how often have you felt that you were unable to control the important things in your life?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

3. In the last month, how often have you felt nervous and "stressed"?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

4. In the last month, how often have you felt confident about your ability to handle your personal problems?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

5. In the last month, how often have you felt that things were going your way?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

6. 4. In the last month, how often have you found that you could not cope with all the things that you had to do?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

7. In the last month, how often have you been able to control irritations in your life?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

8. In the last month, how often have you felt that you were on top of things?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

9. In the last month, how often have you been angered because of things that were outside of your control?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

10. In the last month, how often have you felt difficulties were piling up so high that you could not overcome them?
___ 0 = never ___ 1 = almost never ___ 2 = sometimes ___ 3 = fairly often ___ 4 = very often

Appendix F: In-Lab Visit Data Collection Form

Freshman Health Study
Data Collection Form
Version 7/23/2020

Subject ID: _____
Date: _____
Staff Initials: _____

Visit: □ Baseline □ End of Study

Participant fasted at least 8 hours? □ Yes No

If the participant has not fasted, reschedule the appointment

BLOOD PRESSURE

Participant should rest with feet flat on ground for 5 minutes prior to measurement. Take 3 readings.

Use left arm for measurement unless this arm cannot be used. If the right arm is used, please indicate why below

1) _____ 2) _____ 3)_____

PHYSICAL MEASURES

Height (cm) _____ _____

Weight (kg) _____ _____

The 2 height measures must be within 0.5 cm. If >0.5 cm difference, take a 3rd measure

The 2 weight measures must be within 0.5 kg. If >0.5 kg difference, take a 3rd measure

Waist (cm) _____ _____ _____

The 2 waist circumference measures must be within 0.5 cm. If >0.5 cm difference, take a 3rd measure

BLOOD SAMPLE

Time sample was acquired _____

SUPPLEMENTARY TABLES

Supplementary Table 1: Results of t-tests Comparing Visit 1 and Visit 2

	Mean (SD) at v1	Mean (SD) at v2	T(df)	95% CI	p
BMI	23.48 (3.70)	24.07 (3.62)	-3.56 (109)	-0.92, -0.26	**<.001***
Waist circumference	77.24 (10.16)	78.71 (9.78)	-5.05 (102)	-2.01, -0.88	**<.001***
Clinically depressed	N=18	N=22	-1.07 (109)	-0.10, 0.03	.287
Sleep quality	5.23 (2.29)	5.90 (2.50)	-3.06 (109)	-1.11, -0.24	**.003***
Physical activity	55.92 (45.6)	51.10 (39.69)	0.94 (106)	-4.84, 13.61	.348
Perceived stress	21.08 (3.68)	20.63 (3.66)	1.32 (107)	-0.25, 1.23	.191
Alcoholic drinks consumed per week	4.31 (5.32)	4.93 (6.11)	-1.99 (100)	-1.70, -0.004	**.049***
Circulating IL-6	0.44 (1.76) [a]	0.44 (1.61) [a]	1.36 (89)	-0.03, 0.15	.176
Circulating IL-1β	0.05 (2.08) [a]	0.03 (2.89) [a]	1.87 (89)	-0.001, 0.03	.065
Circulating IFN-γ	3.69 (2.16) [a]	3.88 (2.01) [a]	-2.03 (89)	-2.03, 3.56	.589
Stimulated IL-6	145.92 (74.23)	153.99 (74.3)	-0.55 (89)	-18.39, 10.40	.583
Stimulated IL-1β	169.43 (97.55)	202.01 (109.32)	-2.64 (89)	-41.53, -5.82	**.010***
Stimulated IFN- γ	1.57 (2.58) [a]	1.94 (2.17) [a]	-0.03 (89)	-0.78, 0.75	.970
Number of MetS criteria met	0.31 (0.62)	0.46 (0.71)	-2.39 (100)	-0.24, -0.02	**.019***
MetS Symptom Severity, excluding Asian participants	-0.35 (0.68)	-0.18 (0.68)	0.178	5.435 (79)	**<.001***

Note. SD, standard deviation; df, degrees of freedom; CI, confidence interval; BMI, body mass index; MetS, Metabolic Syndrome; IL, interleukin; IFN, interferon; clinical depression defined as BDI-II score >16; [a]for non-normally distributed variables, values are presented as geometric means and geometric SDs; * $p < .05$

Sensitivity Analyses: Removing Asian participants from Metabolic Syndrome Symptom Severity Analyses

Supplementary Table 2: Correlations between Metabolic Syndrome (MetS) Symptom Severity and Diet Quality, Circulating Cytokines, and Stimulated Cytokines at Each Visit, Excluding Asian Participants

		MetS Symptom Severity	
	df	*r*	*p*
Diet quality (visit 1)	80	-.424	**<.001***
Diet quality (visit 2)	78	-.464	**<.001***
Circulating cytokines (visit 1)	76	.087	.451
Circulating cytokines (visit 2)	67	.267	**.026***
Stimulated cytokines (visit 1)	76	.078	.498
Stimulated cytokines (visit 2)	67	.075	.543
Change in diet quality	78	-.136	.228

Note. MetS, metabolic syndrome; df, degrees of freedom; * $p < .05$

Supplementary Table 3: Results of Regression Analyses Testing the Concurrent Association between Diet Quality and Metabolic Syndrome (MetS) Symptom Severity at Each Visit; Excluding Asian Participants

	B (*SE*)	*p*	R^2 (adj. R^2)
Test whether diet quality predicts MetS symptom severity at visit 1, with sleep quality, physical activity, and perceived stress included as covariates (df = 76)			
Diet Quality	-0.024 (0.006)	**<.001***	0.196 (0.154)
Sleep Quality	0.001 (0.031)	.965	--
Physical Activity	-0.001 (0.002)	.745	--
Perceived Stress	-0.001 (0.021)	.960	--
Test whether diet quality predicts MetS symptom severity at visit 2, with sleep quality, physical activity, and perceived stress included as covariates (df = 75)			
Diet Quality	-0.024 (0.005)	**.001***	0.261 (0.222)
Sleep Quality	-0.014 (0.027)	.613	--
Physical Activity	0.003 (0.002)	.097	--
Perceived Stress	0.024 (0.018)	.190	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; * $p < .05$

Supplementary Table 4: Results of Regression Analyses Testing the Association between Circulating Cytokines and Metabolic Syndrome (MetS) Symptom Severity at Each Visit, Excluding Asian Participants

	B (*SE*)	*p*	R^2 (adj. R^2)
Test whether circulating cytokines predict MetS symptom severity at visit 1, with sleep quality, physical activity, and perceived stress included as covariates (df = 72)			
Circulating Cytokines	0.020 (0.030)	.500	0.025 (-0.029)
Sleep Quality	-0.035 (0.032)	.288	--
Physical Activity	-0.001 (0.002)	.635	--
Perceived Stress	0.015 (0.022)	.488	--
Test whether circulating cytokines predict MetS symptom severity at visit 2, with sleep quality, physical activity, and perceived stress included as covariates (df = 64)			
Circulating Cytokines	0.058 (0.026)	**.031***	0.100 (0.044)
Sleep Quality	-0.026 (0.031)	.419	--
Physical Activity	0.002 (0.002)	.336	--
Perceived Stress	0.014 (0.021)	.503	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; MetS, metabolic syndrome; * $p < .05$

Supplementary Table 5: Results of Regression Analyses Testing the Association between Stimulated Cytokines and Metabolic Syndrome (MetS) Symptom Severity at Each Visit, Excluding Asian Participants

	B (*SE*)	*p*	R^2 (adj. R^2)
Test whether stimulated cytokines predict MetS symptom severity at visit 1, with sleep quality, physical activity, and perceived stress included as covariates (df = 72)			
Stimulated Cytokines	0.036 (0.031)	.249	0.037 (-0.017)
Sleep Quality	-0.035 (0.032)	.285	--
Physical Activity	-0.001 (0.002)	.505	--
Perceived Stress	0.015 (0.022)	.489	--
Test whether stimulated cytokines predict MetS symptom severity at visit 2, with sleep quality, physical activity, and perceived stress included as covariates (df = 64)			
Stimulated Cytokines	0.016 (0.033)	.633	0.035 (-0.026)
Sleep Quality	-0.039 (0.032)	.225	--
Physical Activity	0.001 (0.002)	.610	--
Perceived Stress	0.012 (0.022)	.596	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; MetS, metabolic syndrome

Supplementary Table 6: Results of Regression Analyses Testing the Association between Change in Diet Quality and Metabolic Syndrome (MetS) Symptom Severity at Visit 2, Excluding Asian Participants

	B (*SE*)	*p*	R^2 (adj. R^2)
Test whether change in diet quality predicts MetS symptom severity at visit 2, with sleep quality, physical activity, and perceived stress included as covariates (df = 75)			
Change in Diet Quality	-0.010 (0.007)	.168	0.032 (-0.014)
Sleep Quality	-0.018 (0.031)	.556	--
Physical Activity	0.001 (0.002)	.490	--
Perceived Stress	0.022 (0.021)	.298	--

Note. SE, standard error; df, degrees of freedom; adj., adjusted; MetS, metabolic syndrome

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