COMPARISON OF METABOLIC AND ANTIOXIDANT RESPONSES TO A BREAKFAST MEAL WITH AND WITHOUT PECANS

by

ALEXIS R. MARQUARDT

(Under the Direction of Jamie A. Cooper)

ABSTRACT

Substitution of butterfat with tree nuts in meals may provide metabolic protection, although responses among males and females is unknown. Our objective was to determine postprandial responses in triglycerides, glycaemia, appetite, and antioxidant capacity from a high saturated fat (SFA) meal containing butter vs. partial substitution of butter for pecans (28g) in adult males (n=10) and females (n=12). This was a double-blind, randomized control trial with two testing visits involving consumption of the control (high SFA) vs. pecan meal. Blood draws, and a visual analog scale for appetite, were taken at fasting and intermittently for 3h postprandially. Triglycerides ($p=0.02$) and lipid peroxidation ($p=0.02$) were suppressed more, and antioxidant capacity increased more ($p=0.05$), for pecan vs. control in males, but not females. Conversely, females, showed improved satiety ratings ($p<0.05$) following the control vs. pecan meal. Partial substitution of butter with pecans in a breakfast meal positively affected several health-related biomarkers in males.

INDEX WORDS: CARDIOVASCULAR DISEASE, SATURATED FAT, TREE NUTS, PECANS, GLYCEMIA, TRIGLYCERIDES, ANTIOXIDANTS

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ALEXIS R. MARQUARDT

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ALEXIS R. MARQUARDT

Major Professor: Jamie A. Cooper
Committee: Chad M. Paton
Lynn B. Bailey

Electronic Version Approved:

Ron Walcott
Interim Dean of the Graduate School
The University of Georgia
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DEDICATION

I would like to dedicate this work to my parents, for supporting me every step of the way throughout my academic achievements.

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I would like to extend the greatest of thanks to my major professor, Dr. Jamie A. Cooper, and my committee members, Dr. Chad M. Paton, and Dr. Lynn B. Bailey, for all critiques, guidance and contributions to this project. I would additionally like to thank all present and past members of the Human Nutrition Laboratory for their assistance in data collection, entry, and analysis for this project. Finally, I would like to thank my parents, in-laws, and my husband for encouraging, and supporting me in my adventure to pursue a Master's in nutrition.

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CHAPTER 1

INTRODUCTION

Chronic diseases such as cardiovascular disease (CVD), type II diabetes, and certain cancers account for nearly 60% of all deaths. This percentage is projected to escalate to 73% by 2020 [1]. Some modifiable risk factors for these chronic diseases include elevated blood lipids, poor glycemic control, and high oxidative stress [2]. To combat these chronic disease risk factors, lifestyle changes in diet and nutrition are necessary. While it has been concluded that long-term dietary interventions are successful in altering and improving the risk factors associated with these chronic diseases, acute studies have also demonstrated similar results [3-6]. The short-term effects of individual foods can not only improve health-related indices, but also help to mitigate the detrimental effects of foods that can worsen markers of health [7].

The average diet among U.S. adults is high in simple sugars and saturated fatty acids (SFA) which can act as an obstacle to healthy eating. Similarly, the typical American breakfast often contains those high amounts of sugar and saturated fatty acids (SFA) and can also be devoid of fiber, unsaturated fatty acids (USFA), vitamins, minerals and other nutrients [8]. This leads to decreased satiation and increased postprandial blood glucose and lipids, which can contribute to weight gain, obesity, and additional risk factors for the development of chronic disease [9-12].

Conversely, tree nuts are a rich source of many nutrients that provide beneficial health affects in humans. Many tree nuts, including walnuts, almonds, and pecans, are known for their

favorable fatty acid profiles. High in USFAs, tree nuts have been shown to improve fasting blood lipids and suppress the postprandial increase of blood lipids following meal ingestion [13-16]. Tree nuts are also a rich source of fiber, which has been shown to reduce the prevalence of some cancers and improve satiety [17, 18]. In addition to the health benefits of a high fiber content and fatty acid profile, tree nuts provide the body with antioxidants. Rich in different antioxidants, tree nuts aid in reducing lipid peroxidation and increasing total antioxidant capacity ultimately limiting the amount of oxidative stress in the body [3, 4, 19, 20].

Pecans are a rich source of monounsaturated fatty acids, fiber, and other essential nutrients [21]. While there is limited health-related research on pecans, supplementation within the diet has been shown to improve blood lipids, lowering the risk for atherosclerosis and CVD [5, 22]. Additionally, compared to other tree nuts, pecans contain the highest level of antioxidants [23]. Past studies have shown through both dietary interventions and acute meal challenge studies that pecans increase antioxidant capacity and decrease lipid peroxidation in plasma [3, 20]. Additionally, tree nut consumption has been shown to produce differences in health-related outcomes in males and females [24, 25]. However, potential differences in how men and women respond to acute pecan consumption in a number of health-related biomarkers has yet to be determined.

Therefore, there are two aims to this thesis: Aim 1) to compare the postprandial health effects of blood lipids and glycemia of a standard (SFA-rich) breakfast muffin to a muffin with a partial substitution of SFA for 1 ounce (28g) of pecans in males and females separately. Aim 2) to compare the plasma antioxidant and appetite responses of the standard (SFA-rich) breakfast muffin to the pecan-containing muffin. The results of this study could have important clinical applications as it may determine if simple substitutions, such as pecans for a SFA-rich food

source like butter, will mitigate the negative postprandial effects of a typical American breakfast on blood lipids, glycaemia, and oxidative stress while also improving appetite measures.

Chapter 2 (Literature Review) outlines relevant topics concerning this thesis project including chronic disease, chronic disease risk factors, (ie blood lipids, glycemia, oxidative stress and appetite) health-related differences between sexes, and the role tree nuts have on improving the aforementioned disease risk factors. Chapter 3 is comprised of the manuscript examining the impact of 1 oz (28g) of pecans in a breakfast muffin on blood lipids, glycemia, oxidative stress, and appetite within a healthy population of males and females. For aim 1, we hypothesize that males and females will respond differently to the two test meals, with males showing lower postprandial blood lipids, glycaemia, and lipid peroxidation of the pecan-containing muffin compared to the standard breakfast muffin. Additionally, for aim 2, we hypothesize that the pecan-containing muffin will lead to increased plasma antioxidant levels and improved appetite compared to the standard breakfast muffin in both males and females. Chapter 4 contains a brief summary and conclusions of this thesis.

CHAPTER 2

REVIEW OF LITERATURE

Dietary Fat

There are three essential macronutrients in the human diet: protein, carbohydrates, and fat. Fat is a necessary component of the diet that serves a plethora of vital functions including serving as an energy source that can be stored in large amounts within the body, providing insulation and protection to organs, and producing certain hormones such as adiponectin and leptin [26-28]. Additionally, fat enhances flavor and can provide a degree of satiety [29, 30].

Dietary lipids can be found in three different forms: triglycerides and other types of fatty acids (FA), phospholipids, and sterols [31]. FA vary in terms of the number of carbon molecules present and the presence of double bonds [32]. In total, there are four categories of dietary FAs that are present in our food supply which include saturated FAs (SFAs), trans FAs, and the USFAs, monounsaturated FAs (MUFAs), and polyunsaturated FAs (PUFAs). Each of these FAs have different chemical structures as well as different functional roles in the body. While there are widely accepted understandings of which dietary fats are healthy, there remains to be a universal recommendation about the quantity that should be consumed daily. The dietary recommended intake (DRI) for daily fat intake for adults is between 20-35% of daily energy needs with approximately 10% of daily energy being acquired from longer-chain USFA. Additionally, it is recommended to limit SFAs to less than 10% of daily energy and limit *trans*-fat to as low an amount as possible [33]. The National Academy of Sciences additionally

recommends a daily intake of 12-17g of linoleic acid LA (omega-6 PUFA) and 1-2g of alpha linolenic acid ALA (omega-3 PUFA) [34].

Saturated Fatty Acids

SFAs are lipids that contain a carboxylic acid with a long aliphatic chain comprised of only single carbon-to-carbon bonds. There are no double bonds presents within the FA chain, with each carbon atom bonded to the maximum amount of hydrogen atoms, thus the carbon chain is "saturated" with hydrogen molecules [32]. Therefore, the FA tend to be solid or semi-solid at room temperature. This type of FA is much more stable compared to USFAs (1). SFAs are classified based upon carbon length and categorized into chain lengths: short, medium, long, and very long [35]. Two of the most abundant SFAs are palmitic acid, comprised of a 16-carbon chain, and stearic acid, comprised of an 18-carbon chain. Like all fats, SFAs function primarily as an energy source and insulation to maintain a homeostatic internal temperature. Common food items containing high amounts of SFAs include animal products such as read meat, dairy, and butter. Additional sources of this dietary fat are palm oil, coconut oil, baked good and fried foods [36].

It is widely accepted that diets rich in SFAs can lead to multiple heart health related diseases including cardiovascular disease (CVD), coronary heart disease (CHD), coronary artery disease (CAD), and atherosclerosis [37-48]. The association between SFA consumption and these diseases has been linked to the elevated serum lipid levels that occur with a high SFA diet [49]. However, there have been mixed findings in the literature as to the type or source of SFAs that cause these detrimental health consequences [38]. A meta-analysis of the SFA profile from milk fat revealed a parallel increase in both beneficial and harmful serum lipid levels suggesting that milk fat may not present the same risk for CVD-related diseases as other sources of SFA

[33]. It has been shown that the short and medium chain SFAs are more likely to raise serum lipid levels; whereas, steric acid consisting of an 18-carbon chain has not been shown to increase these blood lipids [39-41].

Unsaturated Fatty Acids

USFAs are very similar in structure to SFAs in that they are comprised of a carboxylic acid with an aliphatic chain consisting of carbon and hydrogen atoms and are classified based upon the length of the carbon chain: short, medium, long, and very long [42]. The major difference between USFA vs. SFA is that an USFA contains at least one double bond in the carbon chain. MUFAs consist of a FA carbon chain with one double bond whereas PUFAs contain two or more double bonds in the carbon chain [38]. Due to the presence of the double bond, USFAs are more chemically reactive molecules and increase in reactivity as the prevalence of double bonds increases [32, 38]. Additionally, the placement of the hydrogen atom around the double bond further classifies the fat as *cis* or *trans*. When the carbon-carbon double bond contains hydrogen atoms on opposite sides, the configuration is called *trans*; whereas when the hydrogen atoms are on the same side, the configuration is called *cis* [38]. *Trans* fats exist both naturally and through chemical modification. Both sources of *trans* fats reveal adverse effects on blood lipid levels [43, 44]. However, more research is needed to determine the health impact of natural *trans*-fat since small amounts of natural *trans,* specifically conjugated linoleic acid (CLA) have found inconsistent results regarding heart disease risk factors [45]. Regardless, the amount of *trans* fat, rather than type, is most important [46]. Common food items containing high amounts of USFAs include plant oils, tree nuts, and fatty fish. Food sources of USFAs tend to be liquid at room temperature due to the *cis* configuration of the hydrogen atoms [46].

There have been over 100 different MUFAs found to exist in nature, most of which are rare compounds [32]. The two most common MUFAs found in our food supply are palmitoleic acid (16:1n9) and oleic acid (18:1n9) [50]. MUFAs are commonly found in foods such as avocados, peanut oil, nut butters, almonds, pecans, and olive oil (OO). MUFA- rich food sources such as OO have been linked to improvements in blood lipids and associated chronic diseases [38, 51].

Similar to MUFAs, there are many different types of PUFAs, which are classified into 12 different families based on double bond position within the carbon chain. The two most important and notable families are the n-6 and n-3, also termed linoleic and alpha-linoleic acid, respectively [32]. The n-6 PUFA, linoleic acid (LA) (18:2n:6), is an 18-carbon chain molecule with two double bonds. This FA is found in nearly every dietary fat and in high abundance in common cooking and vegetable oils such as grapeseed, safflower, sunflower, and soybean oil. In contrast, alpha-linoleic acid (ALA) (18:2n:3), a n-3 PUFA, is an 18-carbon chain molecule with three double bonds [52] This FA is found in highest concentrations within plant oils including flaxseed, soybean, canola, and cottonseed oil. ALA is also found in many other food sources such as fatty fish, chia and flax seeds, nuts, and green leafy vegetables. These two essential FAs, LA and ALA, are crucial to their role in nutrition, body functions, and health since the body cannot synthesize these compounds on its own [53].

Contrary to some of the negative health effects associated with high SFA consumption, USFAs have been linked to positive health-related biomarker effects [33, 37, 38, 47-49, 54, 55]. The 2015 American Dietary Guidelines also recommend replacement of SFAs with USFAs rather than with another macronutrient. While the literature remains divided as to which USFAs will improve plasma lipoprotein levels to a greater degree, both MUFAs and PUFAs have been

shown to produce significant reductions compared to SFAs; however, PUFAs result in greater decrease in total cholesterol [37, 55, 56]. Also, when specifically comparing SFAs replacement with either USFAs or carbohydrates, USFAs produced a greater improvement in serum lipids and lipoproteins [57]. Furthermore, studies have found that an increased USFA intake results in a decreased risk of CHD [38, 58]. In addition to the apparent protective effect against chronic disease risk, USFAs have other beneficial effects including improvement of beta-cell functioning, decreases in inflammation, and improved immune responses [48, 49].

American Diet

Diet quality is critically important for the prevention and maintenance of chronic disease and chronic disease risk. Since almost half of all chronic diseases diagnosed among American adults can be attributed to poor diet, changes to the traditional American diet are pertinent [59]. While diet quality differs by sex, age, ethnicity, income, and education level, problematic areas exist within every demographic. In general, children and older adults have healthier diets compared to young or middle-aged adults. Furthermore, women tend to have healthier diets than men [60]. Regardless, the typical American diet remains high in SFA and processed sugar [61].

To combat the poor dietary quality in the United States, dietary guidelines were created and continue to be revised every 5 years. The current 2015 Dietary Guidelines recommend a diet that focuses on variety, nutrient density, and amount by consuming a variety of vegetables whole fruits, whole grains, and low-fat dairy options [62]. Additionally, there should be limited energy intake from added sugars and SFAs and restrictions on sodium intake. However, based on studies from past recommendations of previous guidelines, lasting behavior changes appear short-lived when following the dietary guidelines [63]. Despite positive efforts to improve diet quality, the American diet quality still falls below the current guidelines, and only dramatic shifts from

current habits would improve diet quality to the standards that are set by the 2015 Dietary Guidelines [64].

Diet quality is in large part influenced by environment and culture. With nearly 82% of US adults dining out at least once a week, diet quality outside of the home should additionally be addressed [65]. Fast food and full service restaurants offer Americans with quick and convenient food options that are associated with higher energy intakes, most notably from total fat, SFA, cholesterol, and sodium [66, 67]. The higher energy intakes are due to the availability of food options, large portion sizing, convenience, consistent marketing, lack of cooking knowledge, and obstacles to healthy eating [68]. Within restaurants, appetizers contain the most energy, fat, and sodium compared to other item types, and children's beverage options contain higher levels of SFA and carbohydrates than adult options [69]. While some fast food chains and full service restaurants offer healthy options, the consensus for overall dietary quality is poor [69]. Additionally, restaurant dining is a cultural aspect of the American life associated with social interaction and leisure. Because of the fast-paced nature of the American lifestyle, the use of these convenient food options is not expected to decrease. However, to combat the poor diet quality found in these food environments, nutrient improvements to food items would be a desirable and advantageous approach.

American Breakfast

While there are no determined percentages of macronutrients or energy that should be consumed for breakfast, it is commonly recommended to consume foods containing lean protein and whole grain [70]. This recommendation is due to the day-to-day variability of energy consumption and macronutrient distribution, as well at the occurrence of daily meals. Researchers in other countries, including Spain and Italy have proposed breakfast quality

guidelines for recommended consumption of food groups, USFA, simple sugar, and total energy intake; however, no guidelines currently exist [70]

While overall American diet quality is poor, the same is not always true for the typical American breakfast. Breakfast consumption in general is associated with positive health-related outcomes such as improved cognition, lower rates of obesity, decreased risk for cardio metabolic risk factors, and improved behavioral components [71-74]. However, when determining the health-related indices of breakfast, studies frequently assess breakfast intake as a whole instead of assessing the effect of cereal and non-cereal options separately [71]. While the most common breakfast items are cereals, other top ten breakfast energy sources in the US diet include cakes, breads, and pastries [61]. When cereal and non-cereal items are categorized separately, non-cereal breakfast items have been associated with higher intake of SFA and lower intake of protein [75].While these items can contribute to the overconsumption of SFA and added sugar, they contain substantial percentages of essential micronutrients including iron, folate, thiamin, riboflavin, and magnesium [61]. Therefore, to avoid the loss of these essential micronutrients, substitution of healthy food ingredients for unhealthy food ingredients are key to improving the overall "health" of breakfast food options.

Tree Nuts

Generally characterized as part of a healthy diet, tree nuts contain numerous nutrients. Common tree nuts include walnuts, almonds, pistachios, Brazil, macadamia, cashew, hazelnut, and pecans. The amount of protein, fat, and carbohydrate differ between nuts; however, fat comprises the main fraction of the macronutrient content followed by protein and carbohydrates respectively [76]. With respect to the type of FA, tree nuts are generally rich in USFAs, which can account for more than 75% of the total FA content [77]. Most of the USFA in tree nuts is

comprised of MUFAs; however, walnuts are also a rich source of omega-3 PUFAs [78]. Although tree nuts are a good source of protein, they do not contain all essential amino acids and are therefore limiting as a complete protein source [76].

Tree nuts also contains dietary fiber, vitamins E and K, folate, magnesium, copper, selenium, and potassium; all of which are essential nutrients commonly consumed inadequately in the diet [76]. They additionally contain phytochemicals such as polyphenols, tocopherols, squalene, and phytosterols. Phytosterols are plant sterols that are constructed similarly to cholesterol. Pistachio and pine nuts contain high amounts of phytosterols whereas walnuts and Brazil nuts contain trace amounts [77]. While the mechanism behind the beneficial effects of phytosterols remains unclear, they can improve immune function and improve blood lipid levels [79]. Phenols, consisting of tocopherols and tocotrienols, are another common component of tree nuts including pecans, almonds, hazelnuts, pistachios, and walnuts [77]. Phenols consist of a variety of compounds including flavonoids, stilbenes, phenolic acids and polyphenolic compounds. Acting as antioxidants, phenolic compounds found in walnuts, pecans, pistachios and hazelnuts aid in combating oxidative stress and free radical damage [77].

Throughout the past decades, numerous studies have been conducted on the effects of tree nut consumption on CVD risk, T2D, and oxidative stress [4, 5, 13-15, 80-85]. The most common tree nuts that have been researched include walnuts, almonds, and pistachios [6, 13, 15, 17, 24, 78, 84-99]. The studies conducted have ranged from month-long dietary interventions [13, 22, 80, 85, 88, 92, 93, 95, 98, 99] to acute meal challenges [6, 17, 20, 86, 97] to determine the impact of tree nut consumption on chronic disease and disease risk factors. While little research has been conducted on pecans themselves, this tree nut contains the highest levels of antioxidants- gamma tocopherol, along with 23 phenolic compounds that have been analyzed in

the pecan [23, 100]. Pecans are also a rich source of USFAs, including both MUFAs and PUFAs (omega-3 and omega-6) [100] and contain about 73g of lipid/ 100g.

Sex as a Biological Variable

While tree nuts have been shown to improve health-related biomarkers such as cognition, blood lipids, glycemia, and inflammation, their effects are not always universal between males and females. [14, 82, 101-104] . Fitschen et al [24] reported no differences between sexes in blood lipid improvement following consumption of 28g of English walnuts over a 4 week period. Conversely, in that same study, consumption of 28g of black walnuts over a 4-week period resulted in differences between males and females. Females experienced increases in total cholesterol, LDL, and HDL following black walnut supplementation, while males experienced decreases. Further, only males had a significantly greater decrease in LDL following consumption of the black walnuts, and a greater increase in HDL following consumption of the English walnuts [24]. Based on this study, it is apparent that males and females may respond differently to tree nuts. In addition to the type of tree nut being important, the frequency of nut consumption could also produce sex differences. Following a 6-year follow-up cohort study, researchers found differences between males and females in association with the risk for metabolic syndrome when consuming the same frequency of nuts [105]. Ultimately, nut consumption was inversely associated with a risk for metabolic syndrome in females; however, this same association was not present in males.

Apart from tree nuts, sex differences have also been found in other studies [106, 107]. Kaviani et al reported differences in angiopoietin-like proteins (ANGPTLs) and TG following a 7-day high-PUFA diet. ANGPTL-3 and -8 in addition to postprandial TG were suppressed in females; however this same improvement was not seen in males [106]. Additionally, following a

4-week isoenergenic Mediterranean diet, men showed improvements in subfractions of LDL particle sizes, whereas this improvement was not observed in females [107]. Therefore, these studies reveal the importance of not only conducting research on a study population consisting of both males and females, but also highlight the importance of factoring sex into the analysis. While males and females do not always respond dissimilarly, it is apparent that in some instances with certain health outcomes, sex can in fact act as a biological variable due to underlying physiological differences between males and females.

While the literature remains sparse when including sex as a covariate in statistical models or when analyzing health outcomes by males and females separately, the practice is occurring more frequently. Multiple researchers have eluded to the necessity of including sex as a variable due to differences in sex hormones or due to the differences in response to treatment [108-110]. Reporting sex effects and analyzing males and females separately can allow researchers additional methods for properly reporting and analyzing data to determine if sex differences are also occurring within a study. [108-110].

Cardiovascular Disease

In recent decades, the attention on heart health has increased due to the elevated presence of heart and blood vessel diseases [111]. Cardiovascular disease (CVD) is the overarching condition for heart related diseases including coronary artery disease (CAD) and coronary heart disease (CHD) as well as other heart conditions such as heart failure, arrhythmia, and heart valve problems. While CHD and CAD are often times used interchangeably, CAD only effects the arteries, whereas, CHD is a direct result of CAD, a condition where both the arteries and heart are affected [112]. CAD, the precursor to CHD, refers to the interaction between excess circulating cholesterol and the arteries. During the formation of CAD, atherosclerosis develops

from the accumulation of plaque within the arterial walls. This process is gradual and occurs over many years or even decades. The accumulation causes the diameter of the vessel to shrink, allowing lower volumes of blood flow within the arteries, increasing pressure, and potentially obstructing blood flow [113]. The can lead to ischemic events, including angina, heart attack, or stroke. Accumulation of plague within arterial walls can be due to an excess amount of cholesterol in the diet, excess energy intake causing obesity, animal fats in the diet (that are rich in saturated fat and cholesterol), and/or the body's inability to correctly and adequately recycle cholesterol [114]. These exogenous and endogenous factors correlate with heart diseases and are often associated with high blood pressure, stroke, heart attack, dyslipidemia, and hypercholesterolemia.

The rise in prevalence of heart related issues has caused CVD to become the costliest chronic disease in America [115]. Based on a recent analysis of medical expenditures associated with CVD, the average annual cost for U.S. adults is $1,104 with a projected expenditure of $15.47 billion nationally. This average is nearly $300 higher per person compared to those without CVD, displaying the added medical cost this chronic disease has on individuals financially [116]. Additionally, there was a gender difference, as men with hyperlipidemia were linked to higher medical expenditures [116]. The majority of medical costs actually cover secondary care following stroke and heart attack, rather than treatments for atherosclerosis and precursor conditions to CVD. Nearly 1.5 million Americans suffer from strokes and heart attacks each year, and that contributes to the $320 billion in annual cost of secondary treatment. Unfortunately, this amount is projected to more than double to $818 billion by the year 2030 [117]. With increases in medical spending, researchers and clinicians continue to seek options to reduce risk development, including changes to the diet.

Just as with any chronic disease, certain individual characteristics and personal choices affect the risk for developing heart related diseases. Some diet or lifestyle risk factors include cigarette smoking, obesity, and consumption of foods high in saturated and *trans* fats [118-122]. The literature depicts an association between CVD risk and diet, especially with FA type. Determining which type of dietary fat is beneficial or harmful to heart disease risk is often confusing, misunderstood, and misinterpreted [123]. Therefore, the controversy regarding dietary fat intake recommendations is often also confusing and constantly evolving. However, it is fairly well documented that CVD mortality and morbidity increase as SFA intake increases [124]. Therefore, many studies have focused on the replacement of SFAs with USFAs, to determine the possible positive health-related biomarker benefits [33, 37, 38, 47, 54]. Replacement of SFAs with USFAs reduces CVD mortality and morbidity through the protective effects of USFA on cardiovascular events [124-126]. This is primarily due to the positive improvements in blood lipid levels after substituting USFAs for SFAs [126]. In addition, the replacement of SFAs with USFAs improves blood pressure, increases circulating endothelial progenitor cells (EPCs), and decreases the number of microparticles [127]. Microparticles are released from endothelial cells and platelets during cell death and regeneration, typical during tissue injury. This risk factor of elevated microparticles in the bloodstream is associated with CVD due to the particles pro-inflammatory and coagulation functionalities [128]. Intake of SFA-rich meals have been shown to cause an acute increase in the circulation of these particles [127]. Conversely, EPCs are known for their protective characteristics to tissue injury by preserving the function and structure of the tissue and are therefore beneficial in increased concentrations [129].

Blood Lipids

As mentioned above, elevated blood lipid levels are a primary risk factor for the development of CVD [126]. Currently high blood lipid levels are attributed to 2.6 million deaths globally according to the WHO [130]. It has been estimated that as little as a 10% decline of cholesterol levels in men over the age of 40 results in a 50% decrease for the risk of heart related disease [130]. Therefore, with an increased prevalence of high blood lipids, there is an increased risk for CVD and other heart related diseases which are now the leading cause of death for women and men [131].

Blood lipids are comprised of many different particles and components including lipoproteins, apolipoproteins, triglycerides (TGs) and cholesterol. While all of these compounds have effects on health-related measures and heart disease, cholesterol is often viewed as the most important blood lipid to monitor and control [132]. Two different lipoproteins- low-density lipoprotein (LDL) and high-density lipoprotein (HDL), define this compound. LDL is associated with plaque accumulation in the arteries and heart disease, whereas HDL is associated with transportation of excess blood lipids for excretion or degradation and can decrease plaque formation.

Cholesterol

A blood test and corresponding lipid panel is the simplest way to determine an individual's cholesterol levels. Total cholesterol (TC) is calculated through an equation that takes into account LDL, HDL and TG concentrations in the blood. Desirable total cholesterol is <200mg/dL with borderline high values ranging from 200-239 mg/dL and high values ≥240mg/dL [133]. Treatment options for high cholesterol include medication use, diet changes, and increased exercise [134]. While energy restriction and exercise regimens can both be

challenging, medication is often used as an easier alternative. The most common medication prescribed to treat abnormal blood lipid levels are statins, which primarily help to reduce LDL through interference of cholesterol production within the liver [135]. However, as with all medications, statins may cause side effects including myopathy, hepatotoxicity, and autoimmune diseases [136, 137]. Because of these adverse side effects, research has continued to search for additional alternatives including diet and bioactive food components that could potentially improve blood lipid levels.

Cholesterol Functions and Synthesis

While high cholesterol levels can cause serious health-related biomarker effects, cholesterol is a necessary component for cell function and stability [138]. It is an animal sterol that is a major precursor for the synthesis of vitamin D, and steroid and sex hormones. It also has additional key functions for brain synapse relations and immune function [139]. Cholesterol is introduced to the body through endogenous (cholesterol synthesis and metabolism) and exogenous factors (consumption of cholesterol through the diet) factors. Cholesterol synthesis begins in the liver through the reaction of acetyl-CoA into mevalonate with the assistance of enzyme HMG-CoA. This is the enzyme that is altered or inhibited by statins to prevent cholesterol synthesis and lower circulating blood cholesterol levels. The other half of cholesterol present within the body is the cholesterol that enters the body through dietary consumption [140].

Lipoproteins

The de novo synthesized cholesterol and dietary cholesterol are both transported through the circulation in lipoprotein particles. LDL is one of two lipoproteins that are commonly measured during blood lipid panels to determine total circulating cholesterol. The normal range

for LDL cholesterol is <130mg/dL, with borderline values of 130-159mg/dL, and high values ≥160mg/dL [133]. This lipoprotein makes up 60-70% of total serum cholesterol, and ranges in size and density with different associations to health based on these classifications [141]. LDL is primarily comprised of cholesterol in addition to phospholipids, and TGs. LDL circulates within the bloodstream until receptor recognition on the surface of hepatocytes for degradation. However, before degradation can occur, LDL can become oxidized, leading to plaque development [142, 143]. These processes result in the unfavorable effects of the development of atherosclerosis, due to the over accumulation of LDL in circulation [144]. The LDL receptor is responsible for recognition of this particle to be taken into the liver and degraded. After degradation, LDL remnants are transformed into bile acids and secreted out of the body via the digestive tract [145].

HDL is a lipoprotein that has a much different structure and function than LDL. This particle is comprised mostly of proteins in addition to cholesterol, phospholipids, and TGs [146]. HDL contributes 20-30% of total serum cholesterol within the blood. The desired range for HDL is ≥50mg/dL, with borderline ranges between 40-49mg/dL, and an undesired level of <40mg/dL [133]. HDL is responsible for reverse cholesterol transport, and is therefore beneficial in higher amounts [147]. This reverse transport refers to the process of cholesterol transport from circulation and peripheral tissues to the liver [148]. Once in the liver, cholesterol is degraded and is excreted from the body through bile salts within the digestive tract.

Triglycerides

The other major component of blood lipid analyses are TGs. This type of ester is a naturally occurring lipid that predominately comprises most dietary fats and oils. Serving multiple functions such as energy supply, energy storage, insulation, and padding, TGs are stored

in the adipose tissue and in lesser amounts in other tissues until needed by the body [149]. This compound is composed of three molecules of one or more different FAs that are bonded to an alcohol glycerol [150]. The desired range for TGs is <150mg/dL with borderline ranges between 150-199mg/dL and high values ≥200mg/dL [133]. Similar to cholesterol, TGs are introduced to the body through endogenous and exogenous pathways.

After ingestion of a meal, TGs are absorbed and re-esterified in the intestinal mucosal cells. TGs are packaged with cholesterol into carrier vessels called chylomicrons and transported through the intestinal lymph, and finally into the blood stream [151]. Since TGs are an insoluble compound, the FA molecules must be detached from the glycerol backbone to allow movement into the cell. In order for TGs to reach specified tissues, lipoprotein lipase (LPL) must hydrolyze free fatty acids from the glycerol backbone. Once fatty acids are taken up into a cell, such as an adipose cell, the FA and glycerol and resynthesized in TGs for storage [152]. Once energy is required, TGs are broken down to a molecule of glycerol and three molecules of FAs. The FAs can be taken up by the targeted cells to provide energy and energy storage. Following hydrolysis, the free fatty acid (FFAs) can travel to desired skeletal and adipose tissue for oxidation or storage respectively [140]. Additionally, the liver synthesizes TGs from free FAs, amino acids, and carbohydrate substrates [150]. The TGs are packaged into very-low density lipoprotein (VLDL) and are transported throughout the blood stream [151]. Similarly, LPL hydrolyzes portions of the TGs present within the lipoprotein to supply the body with free FAs as an energy source or to store them for later use [140]

Just as abnormal levels of lipoproteins within the body can lead to a series of negative health-related biomarker effects, the same can be said of elevated TG levels. Similar to LDL, TGs become a health concern when values are higher than the ideal ranges [153]. However,

unlike LDL and cholesterol, there is weaker evidence for the direct association between elevated TGs and CVD [153]. This is in part due to the metabolism and regulation of these two compounds. Whereas cholesterol cannot be degraded by any cells, TGs can be degraded by most cells [153]. This is due to the natural function of TGs acting as energy sources for a variety of cell types throughout the body. Regardless, elevated TGs have been shown to increase the risk for pancreatitis, and possibly CVD [153]. According to the American Heart Association, there are well known associations between elevated TG levels and CVD; however, the extent to which TGs directly cause CVD remains unclear [154]. It also remains unclear if elevated TG levels act simply as a biomarker, rather than an actual contributing variable to this disease [155]. Irrespectively, there is evidence that abnormally high TG levels are a risk factor for CVD in both men and women in the general public [156]. Despite this conclusion, further research must be conducted to determine if a subsequent decrease in TG levels will directly translate to a decrease in CVD risk.

Tree Nuts and Blood Lipids

As previously mentioned, tree nuts are excellent sources of USFAs, which have been shown to improve blood lipids. A recent review conducted by Del Gobbo et al [14] found that tree nut intake lowers blood lipids including TC, LDL, and TGs; however, the benefits appear to be related to tree nut dose rather than the individual nutrient composition. Greater health-related biomarker benefits were seen with higher tree nut intake [14]. Similarly, an earlier review of blood lipid levels and nuts concluded that dietary intervention studies produced favorable effects [157]. When comparing almonds, peanuts, pecans, and walnuts, modest to large decreases in TC and LDL occurred in those with normal and high cholesterol levels. However, the results were not as robust with macadamia nuts. It was determined that nuts consumed in excess of one and

half servings at least five days weekly elicited the beneficial results for the aforementioned blood lipids [157].

Walnuts, specifically, have been extensively researched. In long-term studies over 6 months, again, favorable effects of blood lipids were determined. Following a one-year randomized control trial through the isocaloric substitution of 15% of energy needs for walnuts, TC and LDL improved, whereas HDL and TGs were no different when compared to the control. In a weight loss study conducted by Rock et al [158], a walnut enriched weight loss diet resulted in TC and LDL decreases. Other long-term dietary studies have also revealed positive improvements in HDL, LDL, TC, and TGs following daily walnut [92, 159, 160]. Regarding shorter term feeding studies of walnuts for 8 weeks or less, the majority of findings report favorable alterations to plasma blood lipids. Two studies that consisted of diets with 18% and 32% energy from walnuts, resulted in decreases for TC and LDL [13, 161]. Following other 8-week diets with daily walnut supplementation reported no changes in blood lipids [91, 162] . In other short-term studies with walnuts, decreases in TC and LDL have been reported [89, 163, 164]. Additionally, short-term diet intervention studies have found favorable effects in other blood lipids, including HDL [165]. Altogether, it appears there is overwhelming evidence that daily walnut consumption improves blood lipid levels in adults.

Similar to the consensus of the positive effects of walnuts on blood lipid levels, almonds have also been extensively studied with respect to blood lipid outcome measures. In several studies, reductions in TC and LDL have occurred [15, 85, 95, 96, 166-169]. Improvements for HDL for similar dietary studies on almonds have also been shown [170]. Conversely, one study by Dhillon et al [171] evaluated the effect of energy deficit diets on body composition and blood

lipids as a secondary analysis. Following a 12-week diet without nuts or a diet with 15% of energy from almonds, no significant difference in blood lipids were reported.

Pistachios and hazelnut diet intervention studies have also shown positive results for blood lipid improvements [15, 98, 172, 173]. After a 12-week supplementation of pistachios, TG levels were significantly lower; however there no differences in TC, LDL, or HDL [98]. Conversely, following a 4-week isocaloric 20% energy replacement with pistachios, TC and TGs were both lowered [173]. Another study supplementing 30g/d of hazelnuts also showed improvements in both LDL and HDL improved by 0.15nmol/L and 0.06 nmol/L, respectively, over a 5-day period [15].

To date, there are only three dietary intervention studies determining the effects of pecans on blood lipids [5, 22, 80]. One study examined the impact of a 4-week diet enriched with 15% of isocaloric substitution of energy for pecans compared to a controlled diet, and only found trends for improvements in blood lipids (TC and LDL) [80]. Another randomized control study revealed a reduction in TC and LDL following an addition of 68g/d of pecans compared to a regular diet after 8 weeks in healthy subjects [22]. However, both of these differences occurred in part because of increases in TC and LDL for the control diet. Finally, Rajaram et al [5] compared a Step 1 diet to a Step 1 diet with a 20% isoenergenic replacement with pecans. While TC and LDL decreased in both diet groups, the Step 1 diet with pecans significantly reduced TC and LDL to a greater degree. It was also noted that the Step 1 diet often causes a decrease in HDL and increase in TGs, both of which were attenuated with the addition of pecans [5].

While the majority of tree nut studies carried out on week or month-long dietary interventions, acute meal challenge studies reveal mixed results for changes in blood lipids. With acute ingestion of walnuts (40g compared to HF meal with olive oil and 75g before and after a

diet intervention), no differences were reported in postprandial blood lipids [86, 162]. Additionally, an acute study determined the effects of consumption of whole walnuts, separate nut skins de-fatted nutmeat, and nut oil on postprandial blood lipids, oxidative stress, and endothelial function. As expected, there was a postprandial increase in TG following consumption of the nut oil and whole nut [6]. Although not a tree nut, a study with peanuts resulted in higher postprandial TGs at 2h and 4h for the control meal compared to the peanut meal [174]. There were no postprandially differences reported for TC, LDL, or HDL. To date, there are no acute meal challenge studies examining the blood lipid responses to meals with and without pecans.

Type II Diabetes

In 2010, it was estimated that 285 million had Type II diabetes (T2D) worldwide, with a predicted increase to 439 million by 2030 [175]. However, analyses that are more recent reveal that the prevalence will be substantially larger. By 2035, T2D prevalence is projected to increase to 592 million [176]. While these increases will be observed worldwide, the prevalence of T2D in developing countries will increase to a greater extent than developed countries [175, 176]. T2D is the most common form of diabetes that develops through the interaction of genetics, epigenetics, and environment. This chronic disease occurs as a result of high blood glucose levels, hyperglycemia, as well a series of steps involving the inability of glucose uptake into cells, insulin insensitivity, and beta-cell dysfunction and failure [177]. Normal or healthy fasting blood glucose levels are <100mg/dL, while prediabetes levels range from 100-125mg/dL, and diabetic levels are classified as ≥126mg/dL after two consecutive measurements within this range [178].Ultimately, maintaining blood sugar control is necessary for proper insulin secretion and glucose uptake, and overall health of bodily functions.

T2D causes an increased risk of hyperglycemia and other chronic diseases and risk factors including dyslipidemia, inflammatory mechanisms, and CVD [179]. While many people do suffer from these conditions, it is noteworthy to mention that many times these diseases co-occur in the majority of the diseased population [180]. A meta-analysis determined that T2D increases the risk for development of other vascular diseases by two-fold, independent from other risk factors [181]. Common risk factors for the development of T2D include hypertension, obesity, fat distribution and weight gain [182] as well as family history, diet, and physical inactivity [183]. Treatment options for T2D commonly include medication use, improvements in diet, and increased exercise which are mainly targeted to manage glucose levels [184]. In a recent meta-analysis, it was concluded that both resistance and aerobic exercise separately, as well as in combination, can have small to moderate beneficial effects on the risk factors for complications for T2D and on glucose control [185].

Because of the presence of co-morbidities, treatment options are continually researched. Individual with hypertension, dyslipidemia, and T2D are often studied to determine what effect different dietary fats have on these diseases. While the association between SFAs and T2D remains unclear, recent evidence reveals USFAs are superior to SFAs in glucose level management to improve glycemic control and aid in nutrition therapy in diabetes [81, 186]. This benefit is proposed to occur through the alteration of the cell membrane and cell signaling caused by the presence of different USFAs [187]. Other speculations for the improvement of T2D through USFAs include increases in FA oxidation, glucose homeostasis and gene expression [188].

Glycemia

Glucose

Glucose is the major metabolic fuel utilized by all tissues, and its availability determines the metabolism of subsequent fuel sources. Through availability and hormonal release, glucose utilization is closely monitored for utilization as storage or energy [189]. In response to blood levels and external stimuli, glucose is regulated through the release of insulin, glucagon, incretin, somatostatin, growth hormone, epinephrine and norepinephrine [190]. For a quick supply of glucose, glycogenolysis occurs. This process involves the cleavage of glycogen for the formation of glucose-6-phostpate (G6P) most notably from skeletal muscle and the liver [191]. The kidney and liver generate additional glucose molecules through gluconeogenesis. This pathway involves the generation of glucose from other metabolites including lactate, and amino acids [192]. In order to generate a useable form of energy, glucose must further be broken down through glycolysis to generate ATP. The remaining compounds from glycolysis can enter the Krebs cycle and oxidative phosphorylation to generate more substantial quantities of ATP for energy [189].

Normal blood glucose concentrations range between 70-140mg/dl and can decrease slightly in the fasted state [193]. When blood glucose levels are higher than the normal, a state of hyperglycemia is achieved. Once a food containing glucose enters the body, taste-receptors in the tongue release hormones promoting the uptake of glucose into cells [194]. Carbohydrate-containing compounds are initially digested by amylase present in saliva, as well as other carbohydrate targeted enzymes, such as glucoamalyase, maltase, sucrase, lactase, and sucrose-isomaltase, on the brush border of the small intestines [195]. In order to enter the enterocytes of the small intestine, glucose must be transported through the SGLUT1 transporter. Once absorbed into the bloodstream, glucose then travels to the liver, kidney and nerve cells [194]. For transport

from the blood into skeletal and cardiac muscle and adipose tissue, the GLUT1 and GLUT4 transporters are utilized [196]. Additionally, the GLUT1 transporter is produced by most cells and functions as a major transporter of glucose to the brain. GLUT2 facilitates glucose transport on the basolateral membrane of the small intestine to allow glucose transport out of the cell into the blood stream and also allows for glucose uptake into the liver [197]. GLUT3 is a high affinity glucose transporter for nerve cells while GLUT5 functions as a fructose transporter [198]. Once glucose is transported to the liver, glucokinase phosphorylates the molecule to generate G6P, which prohibits the expulsion of glucose from the cell. Through another reaction, G6P is converted back into glucose when needed as an energy source. However, this conversion can only occur in the liver, as muscle tissue lacks the specific enzyme (glucose-6-phosphatase) [199]. If, and when, excess glucose is absorbed following a meal, glucose is broken down and converted into fatty acids and stored in the form of TGs via lipogenesis or into glycogen via glycogenesis [200].

Insulin

A number of hormones are responsible for monitoring and maintaining sufficient and healthy blood glucose levels, one of which is insulin. Produced by the beta-cells of the pancreas, this hormone is largely responsible for the regulation of macronutrient metabolism [201]. The main function of insulin is to promote the uptake of glucose from the blood into the liver, fat, and skeletal muscle cells. Additionally, circulating insulin levels determine if the body will be in a state of catabolism or anabolism [201]. When insulin levels are low, catabolism occurs, whereas when insulin levels are high, anabolism occurs. Once glucose is absorbed and blood glucose levels elevate, beta-cells secrete insulin into the blood. This promotes the uptake of glucose through the GLUT4 transporter. Conversely, when blood glucose levels are low, the secretion of

insulin is inhibited. Additionally insulin secretion is inhibited through the release of glucagon by alpha cells within the pancreas [202].

Insulin is produced in the pancreas and is comprised of two protein chains linked by disulfide bonds [203]. Through a series of cleavages and transport packaging, insulin is specifically packaged into mature granules within beta-cells to be released into blood circulation [204]. Insulin is secreted in two phases: rapid and sustained. Once elevated glucose is detected in the blood, the first phase of insulin secretion is initiated. This phase occurs within the first few minutes of detection and involves a rapid surge of insulin release. The second phase of insulin release happens independently of blood glucose levels and peaks a few hours after initial glucose consumption. Once blood glucose levels return to the normal physiological concentration, insulin secretion is terminated [205].

One of the initial signs of T2D is the occurrence of insulin resistance. Insulin resistance is a cell's inability to detect insulin through its insulin receptors. Present within the liver, skeletal muscle, and adipose tissue, insulin receptor defects obstruct the cells from taking up glucose from the blood. This dysregulation causes elevated blood glucose levels to persist generating a state of hyperglycemia, both of which are risk factors for T2D [206, 207]. Therefore, dietary efforts to reduce the glycemic load, decrease the postprandial spike in blood glucose levels, and/or improve insulin signaling are beneficial in the prevention of insulin resistance and hyperglycemia.

Tree Nuts and Glycemia

Due to the positive health benefits associated with tree nuts, their effect on fasting glycaemia and glycemic responses following meal consumption has been heavily studied. However, the findings have been inconsistent [89, 92, 93, 101, 163-165]. Similarly, to blood

lipids, walnuts are the most researched tree nut on this topic. When reviewing studies that have observed the effects of walnuts on glycaemia over a 6-month period or longer, mixed results for changes in HbA1c values occurred. One study with the addition of 30g/d of walnuts reported HbA1c levels decreased at 3 months; however, this effect was erased after 6 months [92]. Conversely, after supplementation of 30g/d of walnuts after one year, weight loss was observed in the walnut group which may have contributed to the improvement in HbA1c; however, a decrease in insulin was found to be independent of the weight loss [93]. Two 8-week long diet with similar supplementation of daily walnuts (48g/d and 43g/d respectively) reported no clinically significant differences in measures of glycemia [164, 165]. A third 8-week study found a significant increase in fasting glucose with 56g/d of walnuts compared to a control diet [163]. In a different 6-week diet intervention of 31g/d of almonds or walnuts, the walnut group revealed a decrease in HbA1c, and an increase in insulin following an oral glucose tolerance test (OGTT), and no significant changes in glucose [89]. Finally a study by Brennan et al [101] evaluated the effect of a four day feeding with 48g of walnuts. No differences in insulin resistance or measures of glucose or insulin occurred.

While walnuts overall show mixed results for measures of glycemia the same observation have been seen in other nuts as well. A mixed-nut diet consisting of walnuts, pine nuts and peanuts compared to a control group reported unchanged fasting glucose and insulin levels [172]. Furthermore, diet interventions including pistachios reveal inconsistent findings [84, 99, 157, 173].

These inconsistent results are also shown for almond interventions; however, there is slightly more compelling data for the positive benefits of this tree nut. In studies over four weeks, improvements to fasting glucose, insulin and HOMA (IR) have been observed [168, 169].

Similarly, the effects of 3-weeks of 30g/d of almonds or sunflower kernels in adults with T2D revealed improvements after completion of both diets. There was a 10% and 11% reduction in fasting blood glucose on the almond and sunflower kernel diet, respectively, with reductions in HbA1c and no change in insulin on either diet [96]. Conversely, in two 4-week dietary interventions involving consumption of 100g/d of almonds compared to a control no differences in glycaemia were reported [95].

To date, only one study has assessed the effects of pecan consumption on glycaemia. This 4-week randomized controlled feeding trial was enriched with a 15% isocaloric substitution of energy for pecans compared to a controlled diet in individuals with overweight or obesity. Following completion of the intervention, insulin, insulin resistance (HOMA-IR) and beta-cell function were significantly improved following the pecan diet compared to the control diet [80]. There were no differences in fasting glucose following diet completion. Based on this initial, but promising data, more research is needed on the glycemic effects of pecan consumption.

Since changes in insulin and glucose occur postprandially, there are more acute studies on this topic compared to cholesterol levels. Two studies found no differences in measures of glycemia following an acute meal containing walnuts or olive oil [86, 93]. Conversely, two studies determining the acute glycemic effect from the addition of tree nuts to white bread vs. white bread alone reported reductions in both glucose and insulin following consumption of the meal with tree nuts compared to bread alone [94, 97] . The acute effect of almonds on glycemia was also assessed through a test meal with a bagel, juice, and butter with or without almonds [208]. Individuals with T2D generated a 30% decrease in postprandial glycaemia following ingestion of the test meal containing 28g of almonds. However, this same magnitude of change was not seen in healthy individuals.

In a review by Kendall et al [209], it is discussed that while the literature remains mixed for the effects of tree nuts and glycaemia in controlling T2D, acute feeding studies minimize postprandial increases in glucose and insulin. Therefore, the acute or postprandial effect of nut consumption may have a more important role than that of chronic nut consumption on fasting measures of glycemia. Regardless of the population in question (healthy or having T2D), the positive association of tree nuts on a blunted postprandial glycemic response is an important health benefit that can minimize chronic disease and chronic disease risk.

Oxidative Stress

Oxidative stress is the precursor to oxidative damage characterized as the imbalance between the production of free radicals and neutralizing capabilities of antioxidants. This common phenomenon, which occurs naturally in the body, helps regulate key inflammatory pathways controlling cell death and differentiation [210]. While not classified as a chronic disease itself, oxidative stress is a chronic disease risk factor associated with obesity, inflammation, T2D, and CVD [210-213].

The role of oxidative stress and its relationship to obesity has been a topic of recent interest. The presence of excess adipose tissue correlates with an increased presence of oxidative stress, which could dysregulate the release of adipokines contributing to chronic disease risk factors associated with T2D and CVD [213]. Oxidative stress is linked to inflammation through poorly understood pathways involving lipid oxidation and mitochondrial function [214]. Oxidative stress can exacerbate both the microvascular and cardiovascular complications of T2D through the activation of five pathways involved in the generation of complications and inactivation of atherosclerotic protective enzymes [210]. While the literature is unclear if oxidative stress contributes to the formation of CVD, growing evidence reveals correlative data

implicating this relationship [212]. Oxidative stress is additionally linked to inflammation and cancer. The process by which oxidative stress can accelerate cancer occurs through activation of inflammatory pathways that promote cell growth and differentiation [211].

Apart from chronic disease, oxidative stress has also been shown to accelerate telomere degradation [215]. Thought to be an evolutionary checkpoint, telomere degradation and therefore gene transcription and translation, would cease preventing replication of mutated or damaged genes. Furthermore, changes in the amount of postprandial oxidative stress has been shown to be influenced by the diet, specifically depending upon different dietary fat sources. One study concluded that differences in FAs elicited minor changes in inflammatory factors following an acute meal [216], and another study was able to determine that a diet rich in MUFAs improved postprandial oxidative stress [217]. Therefore, the FA composition of a meal or diet may influence postprandial oxidative stress although more research is needed.

Antioxidants

Oxidation generates the formation of different reactive species including reactive nitrogen species and reactive oxygen species (ROS) within the body. ROS are oxygen atoms that undergo a removal of an electron, producing a ROS free radical [218]. While free radical formation can be beneficial on the cellular level, over accumulation of free radical ROS can alter DNA, protein, and lipids as well contribute to oxidative stress. Cell injury induced by ROS occurs when there is an imbalance between ROS free radical formation and free radical scavengers [218, 219]. Sources of oxidation can occur through endogenous body systems and exogenous sources. Endogenous systems include metabolism and inflammation, whereas exogenous sources include ultraviolent light damage, smoking, air pollutants, and ionizing radiation [220-222]. ROS free radical oxidative stress can contribute and exacerbate chronic

diseases such as T2D, CHD, cancer, atherosclerosis, hypertension, and autoimmune disorders [223].

In addition, the postprandial state and postprandial lipid oxidation are associated with chronic diseases and corresponding risk factors through the increases of ROS free radical oxidative stress [224, 225]. Lipid oxidation is a naturally occurring process generated through ROS. The ROS attacks the PUFAs within the cellular membranes to quench the missing electron while generating instability and damage to cells [226]. While small amounts of lipid oxidation are beneficial for proper cellular health, increases in this process can be harmful causing cell destruction and death. Increases in lipid oxidation can be exacerbated through consumption of a HF meal due to the elevated circulating TG levels, which cause an increase in lipid oxidation. This increase results in postprandial oxidative imbalance leading to higher oxidative stress [227].

Conversely, antioxidants combat elevated levels of ROS to reduce the risk of CVD, cancer, diabetes, and neurological and immune diseases [228-231]. Antioxidants are any substance that prevents or delays oxidation of another substance through the donation of an electron to stabilize free radicals [231]. If the ROS free radical is stabilized by a free radical scavenger such as an antioxidant, there are fewer attacks on lipid oxidation, preventing cell damage and oxidative stress. Antioxidants can exist as synthetic compounds (i.e. butylated hydroxyanisol, butylated hydroxytoulene, propyl gallate, and tert-burylhydroquinone); however, antioxidants more commonly exist as natural compounds that are typically plant based (i.e. phenolic, polyphenolic, tocopherols, vitamins, minerals and enzymes [232, 233].

Types of Antioxidant Assessment

To measure antioxidant compounds, whether in food sources or in vivo through blood analysis, antioxidant assays can measure three values: total antioxidant capacity (TAC),

antioxidant activity, and antioxidant potential [234]. The most common practice for antioxidant measurement is TAC. This measurement assesses antioxidant status of biological samples and the antioxidant's ability to respond to the production of free radical formation [235].There are two classes of electron transfer that are analyzed to determine this measurement: single electron transport (SET) or hydrogen electron transport (HAT). SET is a two-step process that involves the transfer of an electron and then a hydrogen atom to stabilize the free radial [236]. TAC assays utilizing SET include ferric reducing ability of plasma (FRAP), and trolox equivalent antioxidant capacity (TEAC). In contrast, the HAT method occurs through only the hydrogen atom transfer for stabilization [236]. TAC assays utilizing HAT include oxygen radical absorbance capacity (ORAC), and total radical-trapping antioxidant parameter (TRAP). While all assays measure antioxidant capacity, the literature lacks a validated assay procedure to reliably measure this process in biological food samples [235].

Specifically, the TEAC assay measures antioxidant capacity compared to a Trolox standard, and the TRAP assay measures the capacity of human serum to resist attacks by free radicals. The ORAC assay measures the antioxidant's ability to react with or neutralize free radicals generated in the assay, and the FRAP assay measures the reduction of ferric iron to ferrous iron in the presence of antioxidants. A major difference between assays is the pH in which the reaction is produced. The FRAP assay is acidic which can minimize the potency of the antioxidant's ability to function [235]. In addition, these assays present several limitations including the inability to measure bioavailability or reactivity in situ [235]. Regardless, the ORAC assay has become the assay of choice to measure antioxidant capacity acting through the HAT mechanism.

Lipid peroxidation is another commonly used measurement to determine the amount of antioxidant activity present within human plasma [237]. While ROS can be difficult to quantify, a by-product of lipid peroxidation, thiobarbituric acid reactive substances (TBARS) can be measured instead. While this assay does not directly measure amount of antioxidants present within a sample, it instead measures the amount of lipid peroxidation that occurs through antioxidant activity [237, 238]. TBARS is most notably quantified by the formation of malondialdehyde (MDA). MDA is the end product resulting from lipid peroxidation as it is generated through the degradation of unstable lipid peroxides generated through the attack of ROS free radicals on lipids [239]. Therefore, the higher presence of antioxidants within a sample, the lower the measurable amount of MDA within the sample. In summary, the TBARS assay is known to provide a reliable marker of oxidative stress within the body [238].

Tree Nuts and Oxidative Stress/Antioxidants

In order to combat the negative effects of oxidative stress and lipid peroxidation, bioactive compounds in food sources have been researched to determine if increases in antioxidant ingestion can mitigate the postprandial increases in lipid peroxidation and increase TAC. In long-term dietary intervention studies incorporating tree nuts, the majority of findings reveal that long-term supplementation of antioxidants or antioxidant-rich foods do not cause a lasting change on lipid peroxidation or antioxidant capacity [13, 88, 92, 161, 240, 241]. However, some studies have shown positive improvement in antioxidant capacity and lipid peroxidation. In a 3 month study conducted by Fito et al [242], participants were placed on either a traditional Mediterranean diet (TMD) with olive oil, a TMD with walnuts, or a low-fat diet to determine the impact on lipoprotein oxidation. In both TMD groups, oxidized LDL and MDA

concentrations decreased significantly. A different 4-week crossover study found that a diet with 1.5oz/d of walnuts resulted in significantly higher ORAC levels compared to a control diet [87].

When assessing the impact of tree nuts during acute studies, studies have shown improvements in lipid peroxidation and antioxidant capacity, with most studies being carried out in walnuts and pecans [4, 6, 20, 83, 87, 90]. Following a randomized controlled meal challenge with walnuts, postprandial FRAP values were lower following consumption of the nutmeat compared to the walnut oil or skin. There were no significant differences in MDA concentrations between treatments. In a different study comparing a control meal to a walnut-containing meal, ORAC was 7.5% and 8.5% greater following the walnut meal challenge vs. control for hydrophilic and lipophilic ORAC, respectively. Lower postprandial MDA concentrations were also observed following the walnut meal [83]. Finally, in a randomized crossover trial with test meals containing almonds, walnuts, or control, there was a significant increase in polyphenol concentration and TAC in both nut meals with peak measurements recorded at 90min and 150min postprandially [4].

Compared to other tree nuts, pecans contain the highest levels of polyphenols among the top ten consumed tree nuts [21]. While it has been previously mentioned that pecans contain a favorable FA composition, this tree nut also contains numerous bioactive compounds that can combat chronic disease and associated risk factors [23]. Beneficial compounds include beta-sitosterol, stigmasterol, campsterol, ellagic acid, gallic acid, and epigallocatechin-3-gallateate. Specifically, pecans are a rich source of proanthocyanidins and vitamin E (alpha- and gamma tocopherol) which aid in the prevention of USFA oxidation and oxidative stress [23]. These compounds are thought to be responsible for the majority of the antioxidant capacity measured in pecans [21].

Haddad et al [3] assessed the impact of a pecan-enriched diet on measures of antioxidant capacity and lipid oxidation. Following the 4-week addition of pecans, MDA concentrations deceased 7.4%; however no differences in antioxidant capacity were detected in FRAP or TEAC [3]. When assessing changes in antioxidant capacity and lipid oxidation following the consumption of a pecan-containing meal challenge, the literature reveals positive changes within these measurements. Following a 3-way randomized crossover trial with a 1-week washout period, measures of antioxidant capacity and lipoprotein oxidation were measured [20]. The three test meals consisted of 90g whole pecans and water, 90g pecans blended with water, or a test meal matched for energy, fluid, and macronutrient content. ORAC results revealed minor percent changes in the two pecan test meals of 12% and 10% respectively from baseline. No significant postprandial changes in FRAP were reported. No differences for MDA concentrations were noted either; however, oxidized LDL decreased following the whole pecan test meal.

Appetite Regulation

Appetite is the desire to eat food, and is closely regulated to maintain energy status for metabolic needs. Satiation occurs during a meal and refers to the end of the desire to eat, whereas satiety is the feeling of fullness that occurs following ingestion of meal [243]. For regulation of appetite and satiety to be proficient, there must be proper functioning of the interaction between the brain, digestive tract, and adipose tissue [244]. Appetite regulation and stimulation is heavily researched as it relates to eating behaviors and obesity. With the prevalence of obesity rising beyond 33% percent in the United States, lifestyle changes in food type, meal timing, and increasing fluids are researched to determine possible solutions to appetite regulation [11, 245-248].

Dietary fat remains one of the most heavily researched topics with respect to appetite regulation. Similar to the other macronutrients, dietary fats play a large role in satiation by triggering feelings of fullness through the release of appetite-suppressant hormones [249]. Fat is sensed in the body in both the oral cavity and small intestines of the digestive tract. When dietary fat is detected through FA receptors, hormones such as cholecystokinin, glucagon-like peptide 1, and peptide YY are released to stimulate satiety [244]. In the absence of dietary fat and other macronutrients, the hunger hormone ghrelin is released to generate feelings of hunger. These gut peptides act through vagal afferents as well as through endocrine actions to influence the nucleus tractus solitaries of the brainstem and arcuate nucleus of the hypothalamus to influence feeding behavior [250]. Multiple components of dietary fat have an effect on appetite and satiation including the type/saturation of the FA composition, the FA chain length, and the amount of dietary fat in the diet [251, 252].

Subjective Ratings

There are multiple ways to measure appetite including hunger and satiety hormones (mentioned above), subjective ratings through a visual analog scale (VAS), and/or assessing energy intake [252]. The VAS was developed as a 100mm point line that is anchored on each end by the extremes of the variable being tested [253]. The participant then places a horizontal dash on the line corresponding to the variable in question [254]. The VAS is most commonly used to monitor pain but can also be modified to assess appetite. While the validity of VAS for pain scaling has been well researched throughout the literature, the same can also be said for VAS and appetite [11, 246, 255-259]. Further, subjective ratings of appetite can be challenging to quantify and analyze. However, studies have shown the repeatability of the VAS [255, 256, 260].

Tree Nuts and Appetite Regulation

When comparing the findings for dietary interventions with tree nuts, there are no definitive outcomes on the effect of appetite using subjective ratings with most studies being carried out in walnuts. In a 6 month study by Rock et al [158], the effects of body weight, blood pressure, and satiety were examined in overweight and obese individuals. The participants were randomized into either a weight loss reduced-energy-density diet, or a walnut-enriched-reduced-energy diet (the walnuts supplied 15% of total energy). After 12 weeks, feeling of hunger decreased in the reduced-energy-density diet only, and fullness was lower in the walnut-enriched-reduced-diet [158]. Conversely, in a double-blind cross over trial, participants with metabolic syndrome were randomized to consume a walnut-containing diet of 48g/d of walnuts or placebo that was matched for energy, and carbohydrate and fat content [101]. Every morning consisted of consuming a breakfast shake that was either walnut-enriched or placebo, while participants were fed isocaloric meals for the rest of the day. Following the 4 day trial, feelings of hunger were suppressed while feelings of fullness were amplified following the breakfast shake provided [101]. For almonds, a 4-week randomized control trial showed no changes in appetite ratings following an acute meal challenge [17].

Again, the literature is inconsistent on the effect of tree nuts and appetite during acute studies. Two studies compared the effects of walnuts on ratings of hunger and satiety using a VAS. Both studies concluded that similar ratings were given at all postprandial time points and no differences were observed between dietary fat sources [158, 261]. Specifically, Casas-Agustench et al [261] revealed that after a meal challenge with either 47g walnuts (high in PUFA), olive oil (high in MUFA), or dairy products (high in SFA), there were no differences in ratings of hunger. Additionally, Eastep et al [262] reported no differences in satiety between

meals containing 190 kcals of gummy bears versus 190 kcals of walnuts. Conversely, one acute meal challenge study reported that appetite was suppressed to the greatest degree by the safflower oil and finely ground whole walnuts followed by the low-fat control and walnut oil respectively [263]. Unfortunately, there is no appetite hormone, VAS measures, or energy intake data with acute or chronic pecan consumption.

Summary

As chronic diseases and associated risk factors remain a public health concern, research continues to search for solutions to combat these diseases. While some foods, such as tree nuts have been shown to have positive effects on these risk factors and associated chronic diseases, the majority of research is limited to only a few tree nuts [14, 82]. Tree nuts in general are high in USFAs; however, all tree nuts contain a unique composition of FAs in addition to bioactive food components that can produce different health responses. Due to the favorable FA profile and antioxidant content of pecans, this tree nut may provide additional beneficial improvements in health-related biomarkers that are still unknown [23]. Currently, there are only five clinical studies conducted on pecans that report on blood lipids, glycemia, and antioxidants [3, 5, 20, 22, 80]. Despite minimal research on pecans, these initial studies have reported positive improvements in health-related biomarkers. This indicates that pecans are a beneficial additive to the diet for chronic disease risk and chronic disease. However, since four of the five studies on pecans are long-term dietary interventions, an absolute statement about the acute impact of pecans on human health-related indices cannot be concluded. Therefore, additional research is needed to determine the acute effects of pecan consumption on health-related indices. Results from acute studies will provide additional nutritional knowledge on the beneficial health effects of the pecan.

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CHAPTER 3

COMPARISON OF METABOLIC AND ANTIOXIDANT RESPONSES TO A BREAKFAST MEAL WITH AND WITHOUT PECANS

Marquardt, Alexis. Submitted to the Journal of Functional Foods, June 13th, 2019.

Abstract

Potential physiological differences in acute meal responses to tree nut consumption exist between males and females. **Objective**: To determine the postprandial responses in triglycerides, glycaemia, appetite, and antioxidant capacity from a high saturated fat (SFA) meal versus a meal with partial substitution of SFA for pecans in adult males and females. **Methods**: This was a double-blind, randomized control trial with 22 healthy adults (n=12 females, n=10 males). There were two testing visits involving consumption of a control meal containing butter (high SFA) versus a meal with partial substitution of butter with 28g of pecans. At each visit, fasting and postprandial blood draws, and visual analog scales (VAS) to assess appetite, were taken (0, 30, 60, 120, and 180min postprandially). Following meal consumption, subjects also completed a sensory evaluation. **Results**: Postprandial TGs were suppressed for the pecan vs. control meal ($p=0.02$) in males, but not females. Additionally, males, but not females, exhibited an increase in postprandial antioxidant capacity ($p=0.05$) and had an attenuation of the change in lipid peroxidation ($p=0.02$) following consumption of the pecan vs. control meal. For appetite ratings, females showed a greater suppression for change for hunger ($p<0.001$), prospective consumption ($p<0.001$), and desire to eat ($p=0.03$) following consumption of the control vs. pecan meal. There were no changes in measures of glycaemia or sensory evaluation for males or females. **Conclusion**: Partial substitution of butter with pecans in a breakfast meal positively affected several health-related biomarkers in males but not females.es and females.

Key Words: Cardiovascular disease; Saturated fat; Tree Nuts; Glycemia, Triglycerides

Footnote Abbreviations: ANOVA, analysis of variance; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; FA, fatty acids; HNL, Human Nutrition Laboratory; IV, intravenous; MUFA, mono-unsaturated fatty acids; ORAC, oxygen radical absorbance capacity; PUFA, poly-unsaturated fatty acids; RCT, randomized control trial; RIA, radioimmunoassay; SEM, standard error of the mean; SFA, saturated fatty acids; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; TG, triglycerides; USFA, unsaturated fatty acids; VAS, visual analog scale; V1, visit 1; V2, visit 2; WHR, waist-to-hip ratio

1. Introduction

Chronic disease rates continue to rise with cardiovascular disease (CVD) and its associated risk factors remaining the leading cause of death in the United States [1-4]. Elevation of blood lipid levels and uncontrolled glycemic responses are two significant risk factors that contribute to CVD development [5, 6]. Additionally, the postprandial period has been identified as an important time in which chronic disease development can be exacerbated due to higher oxidative stress [7, 8]. This is especially important in today's Western society, since a majority of individuals spend almost two-thirds of the day in a postprandial state [9].

The typical Western diet regularly includes meals that are higher in saturated fatty acids (SFA) and added sugars, and low in fiber and other essential nutrients, thereby elevating chronic disease risk factors and reducing satiety [10, 11]. Several common breakfast meals such as pastries, breakfast sandwiches, and meats can lead to elevated postprandial triglycerides (TG), a glycemic spike, shortened satiety, and increased lipid peroxidation putting the body in a state of postprandial oxidative imbalance which leads to higher oxidative stress [12]. Alternatively, consuming antioxidant-rich foods are believed to combat oxidative stress and have been shown to be associated with a reduced risk of CVD, cancer, diabetes, and neurological and immune diseases [13-17]. Therefore, efforts to improve the nutrient quality of breakfast meals could be used to combat postprandial oxidative stress and improve metabolic health.

With the increasing prevalence of chronic disease and associated risk factors, alternative approaches to medication are becoming more prevalent, especially bioactive food components [18]. Tree nuts are nutrient dense and contain high amounts of unsaturated fatty acids (USFA), fiber, and antioxidants. Several studies have shown that tree nut consumption can generate

beneficial health improvements on blood lipids levels, inflammation, satiation, glycemic control, neurological diseases, and lipid peroxidation [19-24], all of which can reduce chronic disease risk. Interestingly, tree nut consumption does not always lead to similar health outcomes in both men and women, as some studies have shown different outcomes between males and females [25, 26]. Due to treatment-by-sex interactions found within the literature, several studies have alluded to the possible role of sex acting as a biological variable, as well as the importance of factoring sex into analyses to further determine this interaction [27-30].

To date, the majority of health-related tree nut research has been carried out in English walnuts, almonds, and pistachios [31]. Pecans are a rich source of antioxidants, mono-unsaturated fatty acids (MUFAs), protein, fiber, and several vitamins and minerals, and are thought to be associated with similar health improvements as other nuts. Therefore, replacing butterfat in breakfast meals with pecans could be beneficial in reducing chronic disease risk [32, 33]. While there is minimal health research on pecans, initial studies have shown favorable effects on blood lipids, insulin sensitivity, and antioxidant capacity after dietary interventions containing pecans [33-36]. Additionally, Hudthagosol et al. [37] observed an increase in total antioxidant capacity and a decrease in LDL oxidation following an acute meal challenge with pecans. Therefore, the substitution of pecans to a meal could improve acute health responses.

Although initial studies have shown positive effects of pecans, it remains unknown whether the acute effects of pecan consumption are sufficient to overcome the deleterious effects of consuming an energy dense (high SFA, high sugar) breakfast meal in the form of a muffin. The purpose of this study was to examine postprandial responses following consumption of an energy dense breakfast meal rich in pecans versus butterfat in both males and females. Based on other tree nut research in adult males and females [25], we hypothesized that the pecan-enriched

meal would result in a blunted postprandial glycemic response, TG response, and lipid peroxidation response compared to the control meal. We also hypothesized that total antioxidant capacity and satiety would be higher with the pecan-enriched meal in both males and females.

2. Methods

2.1 Study Design

This study was a double-blinded, randomized control trial. Subjects completed two testing visits where they consumed either the control muffin or pecan-enriched muffin meal in a random order. The visits were separated by at least 72 hours. This study was approved by the Institutional Review Board and informed written consent was obtained prior to beginning study procedures.

2.2 Participants

Twenty-two apparently healthy, adult men and women between the ages of 18-45y were recruited to participate in the study. Additional inclusion criteria included having a normal body weight as determined by body mass index (BMI = 18-24.9 kg/m^2). Exclusion criteria included anyone with a chronic or metabolic disease, gastrointestinal disorders or conditions, previous surgeries that could affect swallowing or digestion, medication use, supplement use other than a daily multivitamin, anyone who was pregnant or nursing, or tobacco users. Additionally, anyone with a medically prescribed diet or food allergies related to the ingredients in the test meals including nuts, eggs, or gluten, was excluded.

2.3 Protocol

2.3.1 Lead-in Diet

The day before visit 1 (V1), participants were instructed to follow a 24h lead-in diet consisting of 55-60% carbohydrate, 20-25% fat, and 15-20% protein. A list of sample meals meeting the macronutrient distributions were provided for participants to follow as guidelines. In addition to the meal guidelines for macronutrient distribution, instructions were provided on foods and beverages to abstain from the evening prior to V1 including fruits, vegetables, nuts, nut butters, other foods/beverages containing high levels of antioxidants (green tea and dark chocolate) or foods rich in omega-3 fatty acids (FA) (fatty fish, seafood, flax and chia seeds). Participants recorded everything they ate and drank during this 24h period in a food diary, and these same meals choices, portions, and the food diary were repeated identically the day before visit 2 (V2).

2.3.2 Visit 1

On the day of testing, participants arrived at the Human Nutrition Laboratory (HNL) at 0700 hours following the 8-12h overnight fast and no exercise or alcohol for the past 24h. The 24h food diary completed the day prior to V1 was collected. Anthropometrics including height, weight, blood pressure (BP), and waist and hip circumference were measured. Following baseline measurements, an intravenous (IV) catheter was placed in the antecubital vein for intermittent blood draws and a fasting sample was drawn. The line was kept patent with saline. After the fasting blood draw, participants completed standardized questions regarding appetite using a 100 mm visual analog scale (VAS) [38, 39]. The questions included feelings of hunger, fullness, prospective consumption, and desire to eat. Overall appetite score was calculated as: appetite score = [desire to eat + hunger + (100-fullness) + prospective consumption] / 4 [40].

Participants then completed the breakfast meal challenge by consuming either the control muffin or pecan muffin within a 5-minute period. The muffin recipes were developed using a

nutrient analysis software program (The Food Processor, ESHA Research, Salem, OR), and the nutrient breakdown for each muffin can be found in **Table 1**. The isocaloric breakfast muffins were matched for macronutrients but differed in fat composition. The control muffin contained butter as the primary source of dietary fat while the pecan muffin substituted the majority of the butter for 1 ounce (28g) of pecans (**Table 2)**. Immediately following consumption, a sensory evaluation questionnaire was administered [41]. The 9-point hedonic scale measured consumer acceptance of the muffin based on taste, texture, appearance, smell, and overall acceptance. Eight ounces of water was provided after consumption of the muffin, and again 2 hours later. After ingestion of the breakfast muffin, blood samples and the VAS were taken at 30, 60, 120, and 180 minutes postprandially. Prior to blood sample collection for the postprandial time points, the initial 3 mL of blood/saline was drawn and discarded as waste to ensure all saline was expelled from the line. Upon completion of the 3-hour testing visit, the IV catheter was removed and participants were free to leave the HNL.

2.3.4 Visit 2

For V2, all procedures that took place before and at V1 were repeated. This included completion of the same 24h lead-in diet and food diary as V1, anthropometrics, blood draws, VAS, and the breakfast meal challenge. The only difference between visits was the type of muffin consumed; the participant consumed the other muffin that was not randomly assigned at V1.

2.4 Sample Analysis

For all blood collection, samples were drawn into EDTA vacutainers (Biopool International, Ventura, CA and Greiner Vacuette, Monroe, NC), immediately spun at 3000rpm for 15min at 4°C, and plasma was aliquotted and stored at -80°C until assayed. Plasma insulin

was measured using radioimmunoassay (RIA) kits (Millipore Corp, Billerica, MA), glucose was measured using the glucose oxidase method (colorimetric), and TGs were measured using enzyme-based colorimetric assays (Wako Chemicals USA, Inc., Richmond, VA). For antioxidant analyses, samples were analyzed for their total antioxidant content by oxygen radical absorbance capacity (ORAC) assays (Zen Bio, Inc., Morrisville, NC). Finally, lipid peroxidation was measured using thiobarbituric acid reactive substances (TBARS) enzyme based colorimetric assays (Caymen Chemicals, Ann Arbor, MI).

2.5 Statistical Analysis

A sample size of 20 subjects was estimated to detect a large effect size for antioxidant outcomes based upon a previous study conducted by Hudthagosol et al [37]. The power analysis was calculated using G*Power program 3.1.9.2., assuming at least 80% power (beta) and an alpha set at 0.05. SAS version 9.4 statistical package (SAS Institute Inc, Cary, NC) and GraphPad Prism version 8.0 (GraphPad Software, La Jolla, CA) were used for all data and statistical analyses. Paired t-tests were used to assess differences in nutrient analysis from the food diaries between the two study visits. A Student's t-test was used to assess differences in anthropometric measures between males and females at baseline. A within subject, two factor (treatment and time) repeated measures ANOVA was used to detect main effects and interaction effects for all outcome variables in males and females separately (i.e. not between sexes). When significance was found, post-hoc analyses were conducted using a Tukey's test. Data are presented as means ± standard error of the mean (SEM), unless other stated, and statistical significance was set at $p \leq 0.05$.

3. Results

3.1 Participants

22 adults (n=12 female, n=10 male) completed both study visits and their baseline characteristics are shown in **Table 3**. There were no significant differences for age, BMI, hip circumference, or diastolic BP for baseline measurements between females and males. As expected, height, weight, waist circumference and WHR were significantly higher in males vs. females ($p<0.001$, $p<0.01$, $p=0.02$, and $p<0.01$, respectively), as was systolic BP ($p=0.02$). The nutrient analysis for the 24h lead-in diets showed no significant differences for total energy intake (1,866.5 ± 544.5kcal/d vs. 1,792.8 ± 458.1kcal/d ns) or the distribution of carbohydrate (57.1 ± 5.0% vs. 58.0 ± 4.9%, ns), fat (25.6 ± 4.7% vs. 24.1 ± 3.4%, ns) or protein (17.2 ± 2.5% vs. 17.9 ± 2.9%, ns.) for V1 vs. V2, respectively.

3.2 Physiological responses

The time course of meal response for change in TGs, glucose, and insulin for males and females is presented in **Figure 1**. For TG responses in males, there was a significant main effect of treatment ($p=0.02$) and time ($p=0.03$) but no treatment by time interaction (ns). The significant treatment effect was for greater suppression of postprandial TGs for the pecan vs. control muffin (**Figure 1A**). For females, there was a significant effect of time ($p<0.0001$) but no main effect of treatment (ns) or treatment by time interaction (ns) (**Figure 1B**). For insulin, there was a significant effect of time in both males ($p<0.001$) and females ($p<0.001$) as expected, but no effect of treatment (ns) or treatment by time interactions (ns) (**Figure 1C-D**). Similarly, for glucose there was also a significant effect of time in both males ($p<0.001$) and females

($p<0.001$), indicating that post meal glucose levels rose significantly, but no treatment effects (ns) or treatment by time interactions (ns) (**Figure 1E-F**).

3.3 Antioxidant Measures

The time course of meal response for change in ORAC and TBARS in males and females can be found in **Figure 2.** For ORAC responses in males, there was a significant main effect of treatment ($p=0.05$), indicating that pecan consumption significantly increases plasma antioxidant capacity to attenuate free radical formation compared to control muffins (**Figure 2A)**, but no main effect of time (ns) or treatment by time interaction (ns). Similarly, there was a significant main effect of treatment ($p=0.02$), but no main effect of time (ns) or treatment by time interaction (ns) for TBARS in males. This treatment effect was for greater suppression of lipid peroxidation following consumption of the pecan vs. control muffin (**Figure 2C**). Conversely, for females, there was a significant main effect of time ($p=0.02$) (likely due to a decrease at 180-min post meal), but no effect of treatment (ns) or treatment by time interaction (ns) for ORAC (**Figure 2B**). Further, there were no significant effect of time (ns), treatment (ns), or treatment by time interaction (ns) for plasma TBAR levels in females (**Figure 2D**).

3.4 Subjective Ratings

Subjective VAS responses to the meal challenges for ratings of hunger, fullness, prospective consumption, desire to eat, and overall appetite score in males and females can be found in **Figure 3**. In males, there were no main effects or interaction for any of the VAS measures. However, there was a tendency for lower prospective consumption ($p=0.09$) following the pecan vs. control muffin (**Figure 3E**). Conversely, in females, there was a main effect of time for hunger (**Figure 3B;** $p=0.03$) and overall appetite score (**Figure 3J;** $p<0.001$) and significant treatment effects for hunger (**Figure 3B;** $p<0.01$), prospective consumption (**Figure 3H;**

$p<0.001$) and desire to eat ($p=0.03$). These treatment effects were for greater suppression of hunger, prospective consumption, and desire to eat following consumption of the control vs. pecan muffin. There were no significant treatment by time interactions (ns). Finally, sensory evaluation data for each muffin can be found in **Table 4**. There were no significant differences between muffins for appearance, taste/flavor, texture/consistency, aroma/smell or overall acceptance in either males or females.

4. Discussion

The aim of this study was to compare postprandial responses in a number of health markers to a breakfast meal with and without pecans. Consuming a muffin where butter was partially substituted with pecans led to more favorable postprandial outcomes for male, but not female, participants. Specifically, males had suppression of their postprandial TG response, increased capacity for attenuation of free radical formation, and suppression of lipid peroxidation following consumption of the pecan vs. control muffin. These findings indicate that a pecan-enriched muffin improved postprandial physiological responses compared to a muffin containing butter in healthy adult males.

The different physiological responses to the test meals by sex are similar to other studies in tree nuts or acute meal challenge studies [25, 27]. Fitschen et al [25] reported improvements in blood lipids for black versus English walnuts in males following a 30-day supplementation period, whereas females showed the opposite effect with elevated blood lipids following black walnut supplementation. Further, we have previously shown that 7 days of a high poly-unsaturated fatty acid (PUFA) diet suppressed postprandial TGs in female, but not male,

subjects. Several possibilities exist for why we observed sex-specific differences, such as the presence of bioactive phytonutrients, sex hormones, or the interaction between the two [42]. Since little clinical research has been conducted on pecans, further studies are warranted to determine if a bioactive component(s) or nutrient of the nut differentially influences acute and chronic health measures in males and females and the mechanism behind these differences.

Reducing plasma TG levels has well established health benefits [43-45], and the FA profile of a meal may play an important role in determining postprandial TG levels. As noted in the literature, USFA have been shown to suppress postprandial increases in TG, and this is especially true for PUFAs [27, 46, 47]. Pecans contain a relatively high content of PUFA (nearly 30% of fat energy is PUFA) [48] and have been shown to improve blood lipids in other dietary interventions [34, 35]. Therefore, the suppressed postprandial TG response for males could be due to the higher PUFA content in the pecan muffin. However, this finding could also be attributed to the high MUFA content of the pecan or the higher SFA content of the control muffin as two previous studies have shown that MUFA-rich meals attenuate the postprandial elevation of TGs more so than a SFA-rich meal [49, 50]. Why we observed this TG response for males but not females remains to be determined and should be the focus of future studies.

Postprandial increases in TG levels contribute to oxidative stress through lipid peroxidation [51]. Therefore, TG suppression in our male participants may have led to the decrease in postprandial lipid peroxidation. The observed reduction in lipid peroxidation in our male participants is in agreement with two previous studies in adult men and women following pecan consumption [36, 37] as well as one study with walnuts and almonds [52]. However, it has also been shown that differences in FA composition greatly affects oxidative stress with levels increasing more following consumption of a high SFA meal versus MUFA or PUFA-rich meals

[53]. Therefore, reductions in lipid peroxidation with the pecan-enriched diet can further be corroborated through the FA profile of the pecan vs. SFA-rich control meal.

In addition to a healthy FA profile, pecans are rich in antioxidants, so it was not surprising that the attenuation of free radical formation was seen to a greater degree in the pecan vs. control muffin, although this was only observed in our male participants. This also confirms what has been observed in previous studies with pecan consumption in adults (responses were not examined by sex) [36, 37]. Other studies have also shown improvements in oxidative stress measures following consumption of a test meal with tree nuts when compared to a SFA-rich meal [54, 55]. Interestingly, in our study, the improvement in oxidative stress was only observed in males and could be due to an interaction between sex hormones and the antioxidant capacity of pecans, although this is not yet confirmed [56, 57]. Demirbag et al [58] did evaluate the effect of sex hormones on total antioxidant capacity (TAC), showing that higher TAC values were related to sex hormone levels, and TAC values were reported to be higher in men than women [58]. Therefore, it is possible that the partial substitution of butter for pecans in our study was sufficient to blunt the free radical generation in males but was not quite strong enough for females, especially since the pecan-enriched muffin did still contain some SFA. Following data analysis, additional information regarding birth control usage was obtained from the female participants to determine if synthetic hormones could have had a role in modulating the differences between males and females for the study outcomes. This information can be found in Table 5. Because the majority of female participants were not actively taking hormonal birth control during the study, it is unlikely that hormone medications are responsible for different responses among sexes to the pecan-containing muffins. Therefore, it is more likely that natural

hormone differences between men and women, rather than medications, are responsible for differences in our outcome measures.

With respect to appetite regulation, studies have shown that protein is the most satiating macronutrient [59, 60]. Therefore, the higher protein and fiber content of the pecan vs. control muffin could explain the trend for greater suppression of prospective consumption in males. However, our female participants exhibited greater suppression of hunger, prospective consumption, and desire to eat for the control vs. pecan muffin. It is possible this is due to the FA composition differences between the test muffins, rather than the protein or fiber content, since it has been argued that FA composition has differential effects on appetite [61]. While past studies have shown clear differences on physiological markers of hunger and satiety based on FA composition [61-64], this is not the same for subjective ratings [65]. Some studies reveal that MUFA and PUFA are more satiating than SFA [66, 67]; however, we, and others have shown that SFA can increase ratings of fullness or suppress prospective consumption to a greater degree than USFA [68], especially in female subjects [62]. Therefore, the higher SFA content of the control muffin may have led to lower hunger and prospective consumption ratings in our female participants. We can say, however, that the overall acceptance of the substitution of a nutrient-rich food (pecans) in place a SFA-rich food source is a viable option for consumers based on the sensory evaluations which did not differ between the two muffins.

This study is not without limitations. This was an acute meal challenge study, so the effect following chronic consumption could differ. Another limitation included that the 24h lead-in diet was self-reported food diaries, which could have resulted in omissions of food or other reporting errors. In this study, we also used only one measure of appetite regulation (subjective ratings from a validated questionnaire) with no measure of appetite hormones or subsequent

energy intake. While the administration of the questionnaire is quick and easy for data collection, the reproducibility of the VAS has been shown to provide inconsistent results [69, 70]. Without appetite hormone data or subsequent energy intake data, more research is needed to determine if differences in overall appetite existed between the two meals, and whether males and females respond differently to certain nutrients with respect to appetite. Additionally, while we substituted a portion butter with pecans, it is undetermined if the substitution of another nutrient dense whole food source instead of pecans would produce similar responses. Finally, we had a relatively young, healthy population, so the findings in this study may not be the same in other populations. The aforementioned health benefits observed in this study need to be verified in a more diverse and/or less healthy population.

5. Conclusion

The present findings indicate that males and females responded differently to the substitution of butter for pecans in a breakfast meal on markers of health. Consuming a single muffin with pecans reduced postprandial TG levels compared to the control muffin in males, but not females. Further, males elicited a postprandial diminution in free radical formation and a decrease in lipid peroxidation following consumption of the pecan vs. control muffin. With respect to appetite ratings, females actually had a greater suppression of hunger, prospective consumption, and desire to eat following consumption of the control vs. pecan muffin with no significant differences between test meals in males. Future studies are needed to determine the acute and chronic effects of pecan substitution for SFA and other fat sources, and the potential sex differences in biological responses.

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Table 1. Nutrient Composition of the Muffins

Composition	Control Muffin	Pecan Muffin
Energy (kcal)	720.1	720.3
% Carbohydrate	38.5	40.6
% Protein	4.1	5.5
% Fat	59.1	57.1
Carbohydrate (g)	69.3	73.2
Total Sugar (g)	30.7	31.8
Fiber (g)	2.66	5.38
Protein (g)	7.5	9.8
Fat (g)	47.3	45.5
SFA (g)	28.8	16.7
MUFA (g)	13.8	18.9
PUFA (g)	2.1	7.4
Omega-3 FA (g)	0.7	0.6
Omega-6 FA (g)	1.2	6.6

SFA= Saturated fatty acid; MUFA= Monounsaturated fatty acid; PUFA= Polyunsaturated fatty acid; FA= Fatty acid

Table 2. Nutrient Composition of Pecans versus Butter

Composition	Pecans	Butter
Gram Weight (g)	28.0	28.0
Energy (kcal)	193.5	200.8
% Carbohydrate	7.5	0.0
% Protein	5.0	0.5
% Fat	87.5	99.5
Carbohydrate (g)	3.9	0.0
Total Sugar (g)	1.1	0.0
Fiber (g)	3.5	0.0
Protein (g)	2.6	0.2
Fat (g)	20.2	22.7
SFA (g)	1.7	14.4
MUFA (g)	11.4	5.9
PUFA (g)	6.1	0.9
Omega-3 FA (g)	0.3	0.1
Omega-6 FA (g)	5.8	0.8

SFA= Saturated fatty acid; MUFA= Monounsaturated fatty acid; PUFA= Polyunsaturated fatty acid; FA= Fatty acid

Table 3. Subject Characteristics

	Male (n=10)	Female (n=12)
Age (y)	22.7 ± 3.6	22.6 ± 2.4
Height (cm)	174.9 ± 9.1	163.2 ± 4.3*
Weight (kg)	73.9 ± 9.6	62.4 ± 7.0*
BMI (kg/m^2)	24.1 ± 1.6	23.4 ± 1.9
Waist circumference (cm)	79.9 ± 5.5	74.1 ± 5.2*
Hip circumference (cm)	100.8 ± 5.7	100.5 ± 5.2
WHR	0.8 ± 0.0	0.7 ± 0.0*
SBP (mm Hg)	121.8 ± 12.2	109.8 ± 11.1*
DBP (mm Hg)	72.8 ± 5.7	71.6 ± 9.5
TC (mg/dL)	138.3 ± 28.4	141.6 ± 16.5
LDL (mg/dL)	70.3 ± 20.0	79.2 ± 13.4
HDL (mg/dL)	46.1 ± 8.0	49.0 ± 6.7
TG (mg/dL)	82.7 ± 35.8	68.2 ± 17.1

Values are presented as mean ± standard deviation. BMI= Body mass index; WHR= Waist to hip ratio; SBP= Systolic blood pressure; DBP= Diastolic blood pressure; TC= Total cholesterol; LDL= Low-density lipoprotein; HDL= High-density lipoprotein; TG= Triglycerides.
*Indicates significant difference between males and females at $p<0.05$.
To convert from mg/dL to mmol/L multiply by 0.02586.

Table 4. Sensory Evaluation of Test Meals

	Male (n=10)		Female (n=12)	
	Control Muffin	Pecan Muffin	Control Muffin	Pecan Muffin
Appearance	6.6 ± 0.4	7.2 ± 0.2	7.8 ± 0.3	7.6 ± 0.4
Taste/Flavor	7.6 ± 0.3	7.8 ±0.2	7.7 ± 0.4	8.0 ± 0.2
Texture/Consistency	7.2 ± 0.4	7.2 ± 0.5	7.2 ± 0.5	7.5 ± 0.5
Aroma/Smell	7.4 ± 0.4	7.8 ± 0.3	7.8 ± 0.3	7.7 ± 0.3
Overall Acceptance	7.5 ± 0.3	7.8 ± 0.3	7.8 ± 0.3	7.9 ± 0.2

Values are presented as mean ± standard error of the mean (SEM).

Table 5. Female Participant's Hormonal Birth Control Use During the Study

	Actively on Birth Control?	Type	Brand	Hormones	Dosage
Female Subject 1	Yes	Oral	LoLoestrin	northindrone acetate ethinylestradiol	1mg 10mcg
Female Subject 2	Yes	Oral	Jolessa	levonorgestrel ethinylestradiol	0.15mg 30mcg
Female Subject 3	Yes	IUD	Kyleena	levonorgestrel	19.5mg
Female Subjects 4-12	No	N/A	N/A	N/A	N/A

IUD= Intrauterine device; N/A= Non-applicable

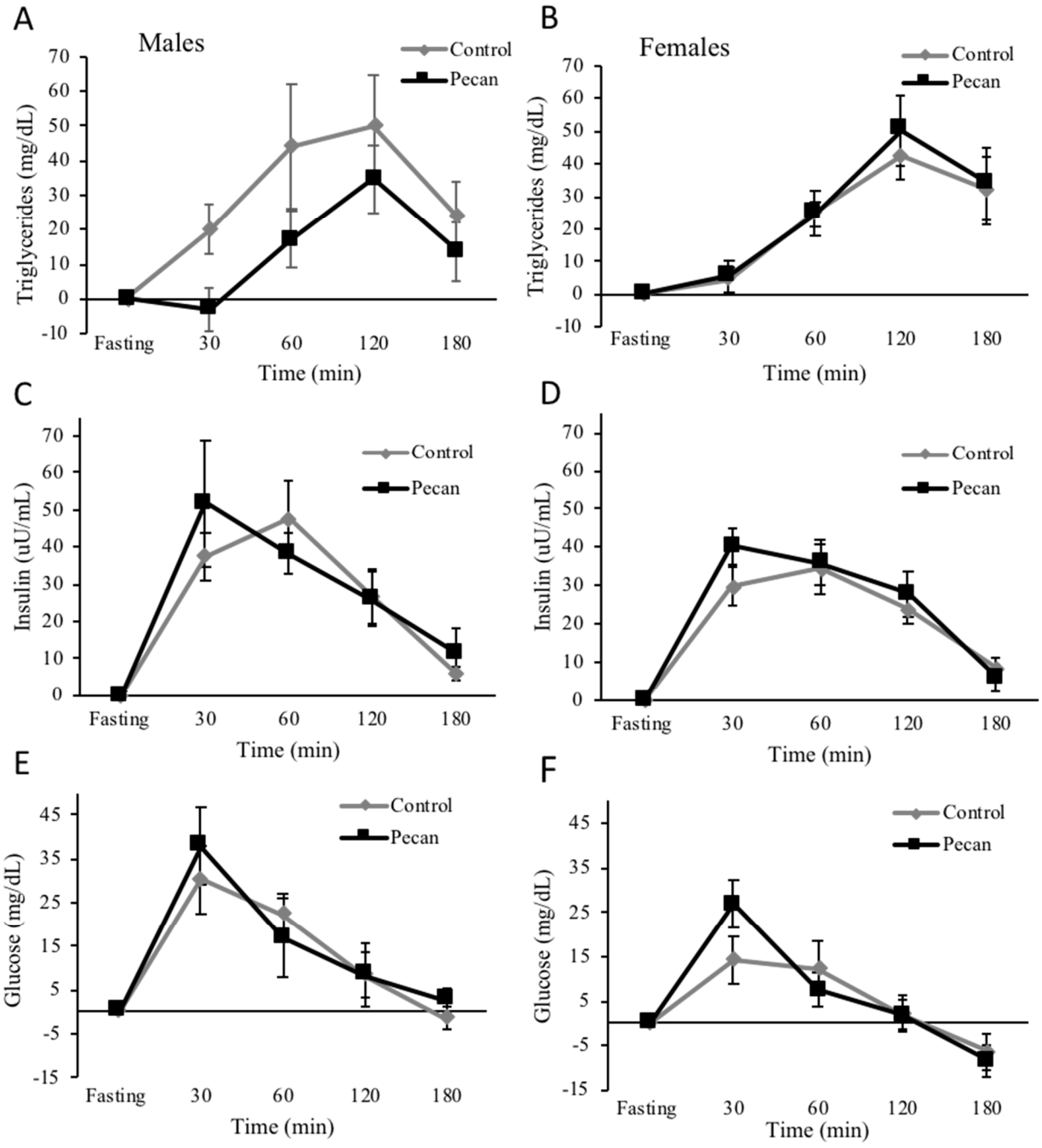


Figure 1. Time course of meal responses for triglycerides (TG), insulin, and glucose for the control versus pecan muffins for males (Figure 1A, C, E) and females (Figure 1B, D, F). There was a significant treatment effect for TG in males with lower postprandial TG for pecan vs. control (p=0.02) (Figure 1B). Error bars represent the standard error of the mean.

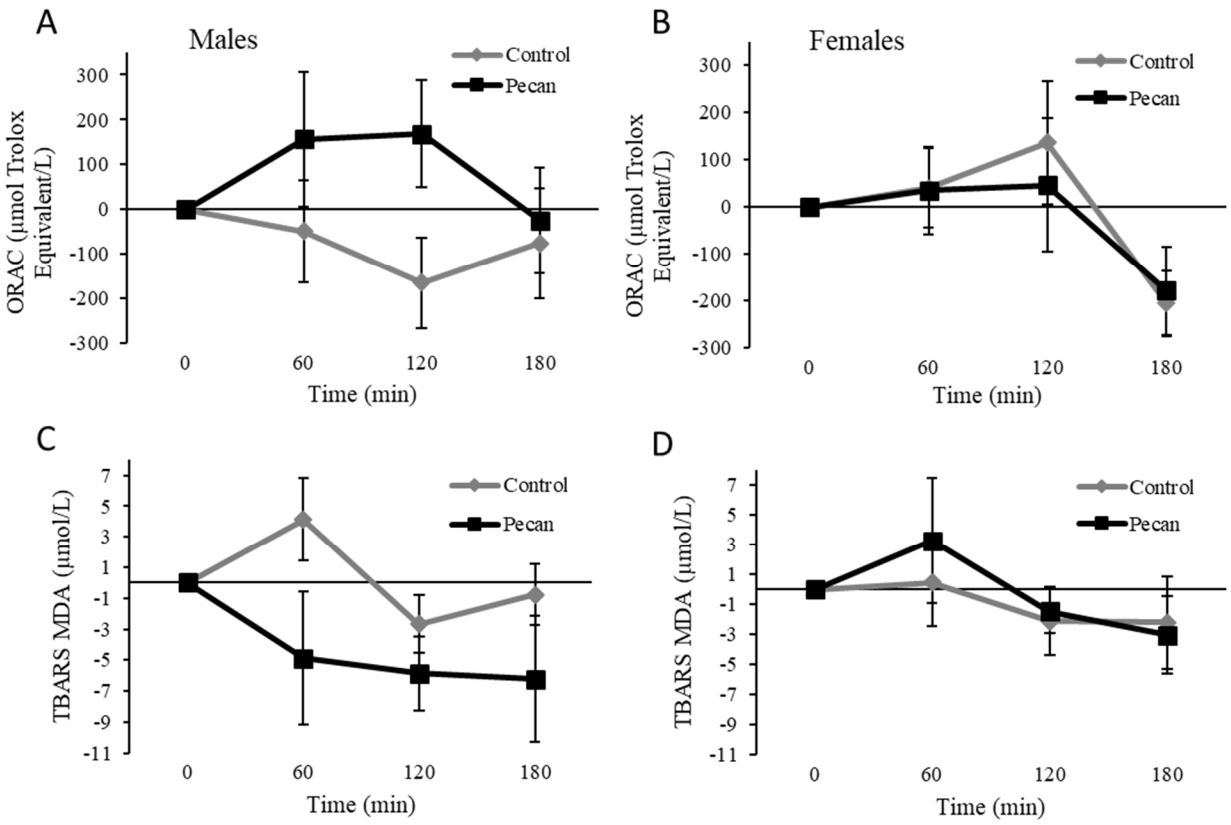
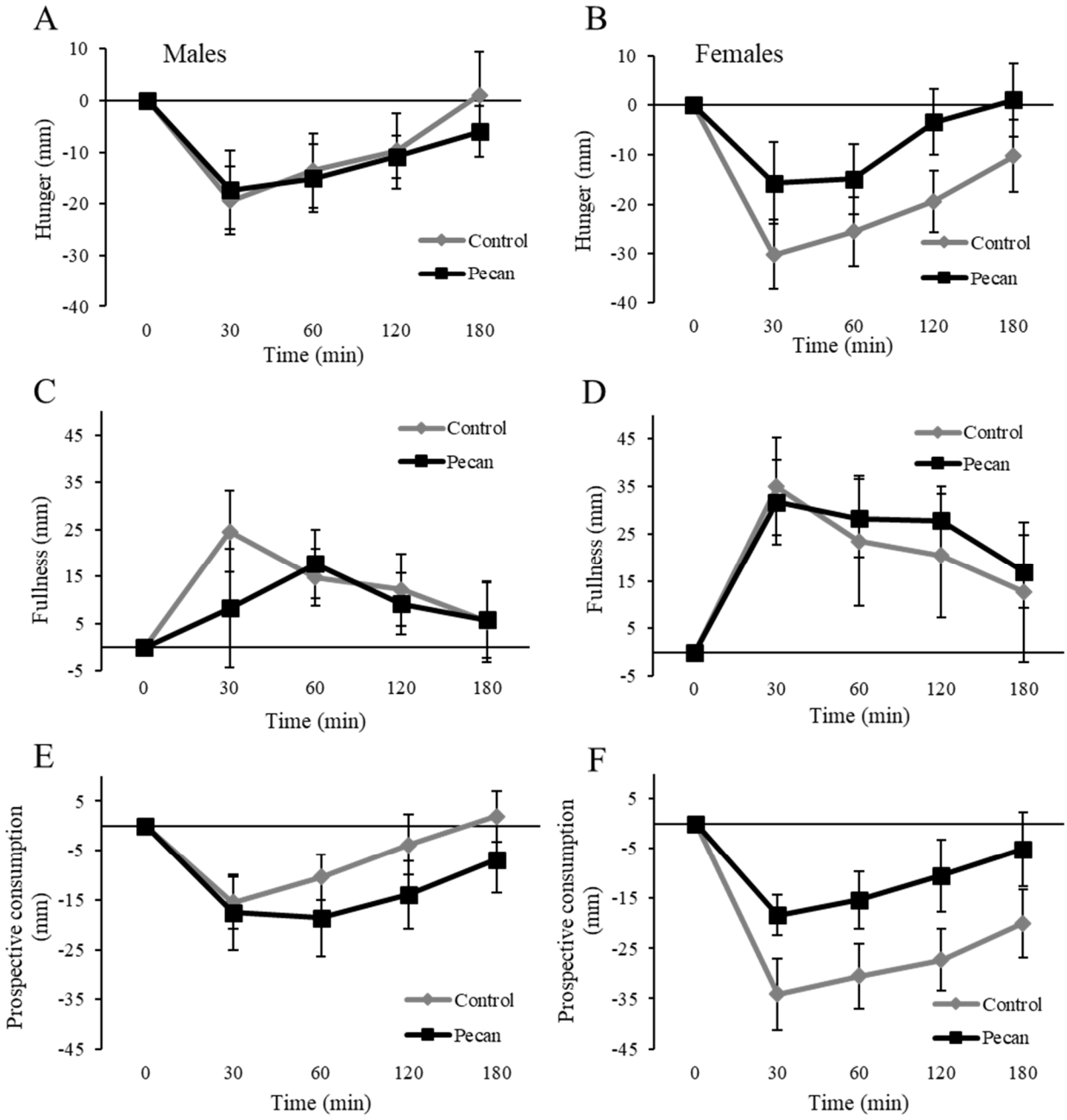


Figure 2. Time course for meal responses for oxygen radical absorbance capacity (ORAC) and thiobarbituric acid reactive substances (TBARS) for the control versus pecan muffins in males (Figure 2A, C) and females (Figure 2B, D). There was a significant treatment effect for higher postprandial ORAC for pecan vs. control (p=0.05) (Figure 2A) and lower postprandial TBARS for pecan vs. control (p=0.02) (Figure 2C) in males. Error bars represent the standard error of the mean.


A
Males
Hunger (mm)
10
0
-10
-20
-30
-40
0
30
60
120
180
Time (min)
Control
Pecan
B
Females
Hunger (mm)
Time (min)
Control
Pecan
C
Fullness (mm)
45
35
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Time (min)
Control
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D
Fullness (mm)
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Control
Pecan
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Prospective consumption (mm)
5
-5
-15
-25
-35
-45
Time (min)
Control
Pecan
F
Prospective consumption (mm)
Time (min)
Control
Pecan

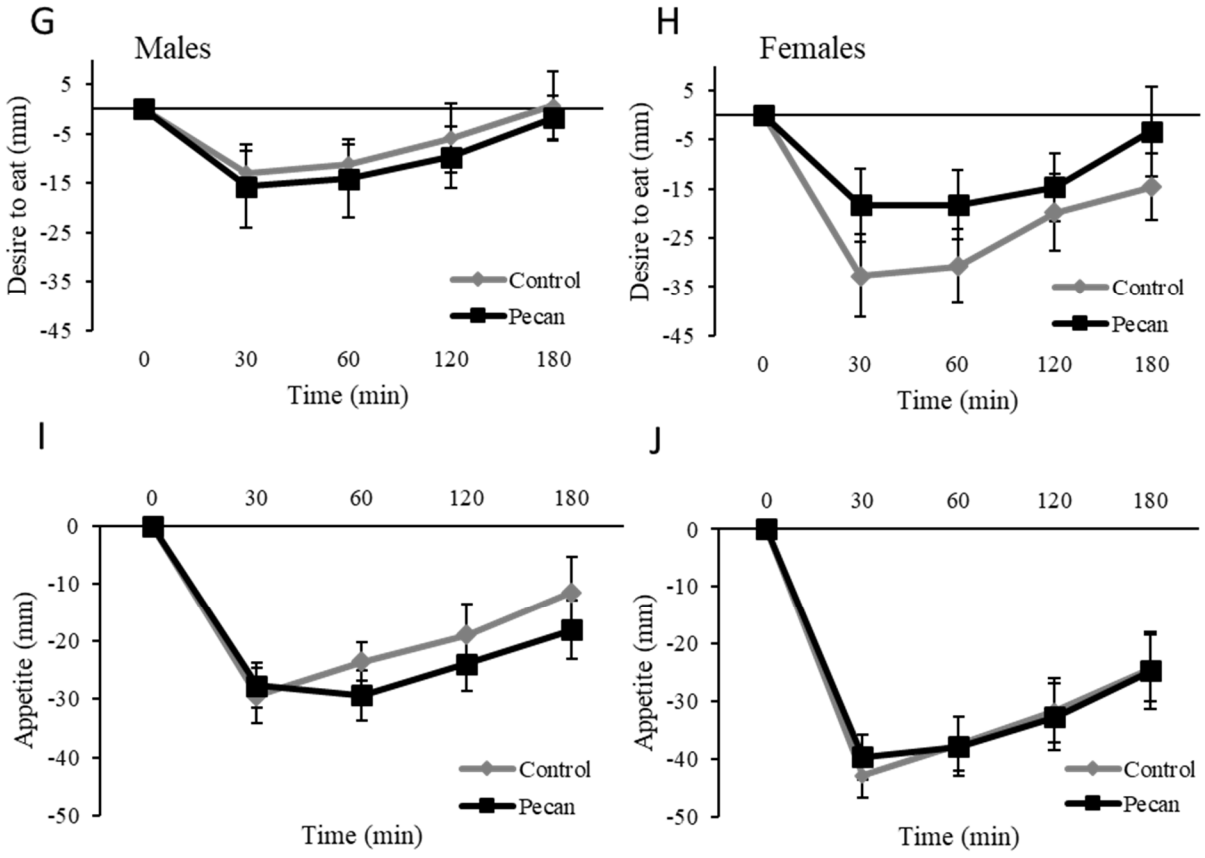

Figure 3. Time course for meal responses for visual analog scale (VAS) responses regarding hunger, fullness, prospective consumption, desire to eat, and overall appetite score for the control versus pecan muffins for males (Figure 3A, C, E, G, I) and females (Figure 3B, D, F, H, J). There was a significant treatment effect for greater suppression of hunger ($p<0.001$), prospective consumption ($p<0.001$), and desire to eat ($p=0.03$) in females for control vs. pecan (Figure 3B, F, H, respectively). Error bars represent the standard error of the mean.

CHAPTER 4

SUMMARY AND CONCLUSIONS

Tree nuts are associated with improvements in chronic disease, chronic disease risk factors, and associated health-related biomarkers [19, 20, 34, 36, 52, 71, 72]. However, the majority of research has been conducted specifically on walnuts, almonds, and pistachios, with minimal research conducted on pecans [54, 73-79]. Additionally, while little research exists examining the sex differences between tree nuts, previous research suggests the possible role of sex as a biological variable [25, 80]. Therefore, the overall objective of this study was to determine if pecans would elicit the similar beneficial improvements in health-related biomarkers as other tree nuts and if the effects would differ by sex following an acute meal challenge. Specifically, this study was conducted to compare the postprandial health effects of blood lipids and glycemia of a standard (SFA-rich) breakfast muffin to a muffin with a partial substitution of SFA for 1 ounce (28g) of pecans in males and females separately and to compare the plasma antioxidant and appetite responses of the standard (SFA-rich) breakfast muffin to the pecan-containing muffin.

Previous research on pecans involving long-term diet inventions have shown improvements in blood lipids, glycemia, oxidative stress, and antioxidant capacity [33-37]. While there has been one previous acute study on pecans, the literature lacks an acute study determining the effect of pecans on blood lipids and glycemia following an acute meal challenge. However, differing from the previous acute meal challenge, this project focuses on the partial

substitution of butter (SFA) with 28g of pecans rather than only consumption of pecans compared to a control [37]. Therefore, our study is the first to determine if pecans can mitigate the detrimental postprandial health-related biomarkers following a high-SFA meal through the partial substitution of pecans for butter in a breakfast meal.

The results presented in Chapter 3 revealed different outcomes in males and females for the health-related biomarkers following consumption of the control and pecan-containing meal challenges. There were no differences in total energy, % carbohydrate, % protein, or % fat consumed during the 24-hour lead in diet the day before V1, and V2. Baseline demographics revealed expected significant differences between males and females for height, weight, and WHR. Surprisingly, systolic BP was also significantly higher in males compared to females. Following the pecan-containing meal in males, postprandial TGs were suppressed, oxidative stress was attenuated, and antioxidant capacity was increased. Conversely, these same improvements were not observed in females. Instead, females revealed improved ratings of appetite following consumption of the control meal, while males reported no differences in appetite between the two meals. Additionally, there were no differences reported for measures of glycemia in either males or females. Furthermore, results comparing the sensory acceptance revealed no differences between the two meals for either males or females.

As previously discussed, the differences by sex could be due to differences in hormone levels, or other biological differences not yet determined. Following data analysis, additional information regarding birth control usage was obtained from the female participants and can be found in Table 5. However, the five previous studies conducted on pecans reveal interesting results when focusing on sex [33-37]. Of the five studies that reported improvements in chronic disease risk factors, and associated health-related biomarkers, the majority of the participants

were male. While this is just an observation, and no additionally statistical analyses were conducted on these research studies, this aspect should be taken into account for future studies. Therefore, additional research is warranted to determine if sex has an effect on health-related biomarkers following an acute meal challenge with pecans, as well as in all studies with pecans.

As with any study, limitations did exist. While it is proposed that the sex differences seen following consumption of the meals could be due to differences in hormones, data regarding hormonal contraceptives in the females participants was not obtained. If this information had been collected, a more definitive explanation regarding the sex differences could have been ascertained. In addition, while the control and pecan-containing meals were matched for energy, they were not prepared to supply a specific percentage of daily energy needs based upon the participant's energy needs. As designed, the current study may have overloaded the female participants through total energy and SFA content as to not allow the pecan-containing meal to show any postprandial beneficial differences. Furthermore, due to budget restrictions, the 24-hour lead in diet was not supplied to the participants. While no differences in energy intake, % carbohydrate, % protein, or % fat differed between the 24-hour period prior to V1 and V2, the participants could have made errors or omissions when completing the food diaries. Providing all meals for the 24-hour period would have led to better control over 24h intake by providing the same nutrient content before consumption of the control and pecan-containing muffins. However, in order to ensure total compliance, any meals should have needed to been consumed in the HNL under research personnel supervision.

In conclusion, this was the first study to determine if a partial substitution of pecans (28g) could mitigate the detrimental postprandial effects following consumption of a SFA-rich meal. Additionally, this was the first study with pecans to examine health-related biomarkers

separately by sex. Because sex plays an important role as a biological variable in human research, the hypotheses for this study were set based on the a priori determination to examine males and females separately, and not include sex in the statistical analysis. The results of this study indicate that pecans can improve several of the health-related biomarkers in males, and that sex plays an important role when conducting human studies. However, given the relative good health of the participants, further research is warranted to determine the associated health benefits of pecans in other populations to provide informed recommendations regarding pecan consumption to the general public.

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APPENDICES

APPENDIX A: FOOD DIARY

Participant ID: _____ Week #: _____ Date: _____

Time	Food/Drink	Quantity

APPENDIX B: VISUAL ANALOG SCALE

VAS Questionnaire

Date: _____ Participant ID: _____ Visit: _____ Time: _____
Instructions: For each question, please make an up-and-down line at the point on the line that best describes how you are feeling.

1. ***How hungry are you right now?***
Not at all hungry — Extremely hungry

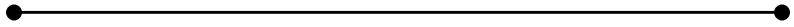
2. How thirsty are you right now?
Not at all thirsty — Extremely thirsty

3. How full are you right now?
Not at all full — Extremely full

4. How nauseated are you right now?
Not at all nauseated — Extremely nauseated

5. How much do you think you could eat right now?
Nothing at all — A large amount

6. How strong is your desire to eat?
Very Weak — Very Strong



APPENDIX C: SENSORY EVALUATION

Sensory Evaluation Form

Recipe Name: Category:

Directions: Check one rating for each of the following: Appearance, Taste/Flavor, Texture/Consistency, Aroma/Smell, and Overall Acceptability

Rating Scale	Appearance	Taste/Flavor	Texture/ Consistency	Aroma/Smell	Overall Acceptability
9. Like Extremely					
8. Like Very Much					
7. Like Moderately					
6. Like Slightly					
5. Neither Like or Dislike					
4. Dislike Slightly					
3. Dislike Moderately					
2. Dislike Very Much					
1. Dislike Extremely					
Office Use Only					
Panelist Code: Date:					

APPENDIX D: NUTRIENT COMPOSITION OF TREE NUTS

Composition	Pecan	Walnut (English)	Almond	Brazil	Pistachio	Hazelnut	Macadamia	Cashew
Gram Weight (g)	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0
Energy (kcal)	193.5	183.1	161.0	183.7	157.4	175.8	190.94	154.8
% Carbohydrate	7.5	7.8	14.1	7.0	18.4	9.9	7.2	20.5
% Protein	5.0	8.7	13.8	8.1	13.5	8.9	4.1	12.4
% Fat	87.5	83.5	72.2	84.9	68.1	81.2	88.7	67.1
Carbohydrate (g)	3.9	3.8	6.1	3.4	7.7	4.7	3.9	8.5
Fiber (g)	3.5	2.4	3.8	2.1	3.0	3.6	3.0	0.9
Protein (g)	2.6	4.3	5.9	4.0	5.7	4.2	2.2	5.1
Fat (g)	20.2	18.3	13.8	18.6	12.7	17.0	21.2	12.3
SFA (g)	1.7	1.7	1.0	4.2	1.6	1.3	3.4	2.2
MUFA (g)	11.4	2.5	8.7	6.9	6.7	12.8	16.5	6.7
PUFA (g)	6.1	13.2	3.4	5.8	3.9	2.2	0.4	2.2
Omega-3 FA (g)	0.3	2.5	0.0	0.0	0.1	0.0	0.1	0.0
Omega-6 FA (g)	5.8	10.7	3.4	5.8	3.8	2.2	0.4	2.2
Total Phytosterols (mg)	44.0	31.6	55.7	26.6	78.1	33.9	52.4	42.0
α-Tocopherol (mg)	1.1	0.2	7.3	1.6	0.5	4.2	0.2	0.3
γ-Tocopherol (mg)	2.3	5.8	0.3	2.2	6.3	nd	nd	nd

Source: US Department of Agriculture Nutrient Database at: https://ndb.nal.usda.gov/ndb/search/list (Accessed on 16 July 2019); Phytosterol composition of nuts and seeds commonly consumed I the United States. J Agric. Food Chem. 2005,53, 9436-9445; the phytochemical composition and antioxidant actions of tree nuts. Asia Pac J Clin Nutr. 2010;19(1):117-123.

APPENDIX E: PHENOLIC COMPOUNDS IN TREE NUTS

Composition	Pecan	Walnut (English)	Almond	Brazil	Pistachio	Hazelnut	Macadamia	Cashew
Gram Weight (g)	28.0	28.0	28.0	28.0	28.0	28.0	28.0	28.0
Anthocyanidins (mg)								
Cyanidin	3.0	0.8	0.7	0.0	2.1	1.9	0.0	nd
Petunidin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	nd
Delphinidin	2.0	0.0	0.0	0.0	0.0	0.0	0.0	nd
Malvidin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	nd
Pelargonidin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	nd
Peonidin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	nd
Flavan-3-ols (mg)								
(+)-Catechin	2.0	0.0	0.4	0.0	1.0	0.3	0.0	nd
(-)-Epigallocatechin	1.6	0.0	0.7	0.0	0.6	0.8	0.0	nd
(-)-Epicatechin	0.2	0.0	0.2	0.0	0.2	0.1	0.0	nd
(-)-Epicatechin 3-gallate	0.0	0.0	0.0	0.0	0.0	0.0	0.0	nd
(-)-Epigallocatechin 3-gallate	0.6	0.0	0.0	0.0	0.1	0.3	0.0	nd
(+)-Gallocatechin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	nd
Flavanones (mg)								
Eriodictyol	0.0	0.0	0.1	0.0	0.0	0.0	0.0	nd
Hesperetin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	nd
Naringenin	0.0	0.0	0.1	0.0	0.0	0.0	0.0	nd
Flavonols (mg)								
Myricetin	0.0	0.0	0.0	0.0	0.0	0.0	0.0	nd
Quercetin	0.0	0.0	0.1	0.0	0.4	0.0	0.0	nd
Isoflavones (mg)								
Daidzein	0.0	0.01	0.0	0.0	0.5	0.0	nd	0.0
Genistein	0.0	0.0	0.0	0.0	0.5	0.01	nd	0.0
Glycitein	0.0	0.0	0.0	nd	0.0	0.0	nd	0.0
Total isoflavones	0.0	0.01	0.0	0.0	1.0	0.01	nd	0.0
Formononetin	0.0	0.0	0.0	nd	0.0	0.0	nd	0.0
Coumestrol	0.0	0.0	0.0	nd	0.0	0.0	nd	0.0

Proanthocyanidin (mg)								
Dimers	11.8	1.6	2.6	0.0	3.7	3.5	nd	0.6
Trimers	7.3	2.0	2.1	0.0	2.9	3.8	nd	0.0
4-6mers	28.4	6.2	7.7	0.0	11.8	19.9	nd	0.0
7-10mers	23.6	1.5	7.9	0.0	10.6	20.9	nd	0.0
Polymers (>10mers)	62.4	5.6	22.5	0.0	34.3	90.3	nd	0.0

Source: US Department of Agriculture Nutrient Database at: https://ndb.nal.usda.gov/ndb/search/list (Accessed on 16 July 2019)

APPENDIX F: PHENOLIC COMPOUNDS IN PECANS AND OTHER FOOD SOURCES

Composition	Pecan	Red Wine	Blueberry	Strawberry	Kale
Gram Weight (g)	28.0	28.0	28.0	28.0	28.0
Anthocyanidins (mg)					
Cyanidin	3.0	0.1	2.4	0.5	nd
Petunidin	0.0	0.6	8.8	0.0	nd
Delphinidin	2.0	0.6	9.9	0.1	nd
Malvidin	0.0	3.9	18.9	0.0	nd
Pelargonidin	0.0	nd	0.0	7.0	nd
Peonidin	0.0	0.4	5.7	0.0	nd
Flavan-3-ols (mg)					
(+)-Catechin	2.0	2.0	1.5	0.9	nd
(-)-Epigallocatechin	1.6	0.0	0.2	0.2	nd
(-)-Epicatechin	0.2	1.1	0.2	0.1	nd
(-)-Epicatechin 3-gallate	0.0	0.0	0.0	0.0	nd
(-)-Epigallocatechin 3-gallate	0.6	0.0	0.0	0.0	nd
(+)-Gallocatechin	0.0	0.0	0.0	0.0	nd
Flavanones (mg)					
Eriodictyol	0.0	0.0	0.0	0.0	nd
Hesperetin	0.0	0.2	0.0	0.0	nd
Naringenin	0.0	0.5	0.0	0.1	nd
Flavonols (mg)					
Myricetin	0.0	0.1	0.4	0.0	0.0
Quercetin	0.0	0.3	2.1	0.3	6.3
Isoflavones (mg)					
Daidzein	0.0	nd	0.0	0.0	0.0
Genistein	0.0	nd	0.0	0.0	0.0
Glycitein	0.0	nd	0.0	0.0	nd
Total isoflavones	0.0	nd	0.0	0.0	0.0
Formononetin	0.0	nd	0.0	0.0	nd
Coumestrol	0.0	nd	0.0	0.0	nd
Proanthocyanidin (mg)					
Dimers	11.8	3.4	1.8	1.5	nd
Trimers	7.3	0.7	1.4	1.6	nd
4-6mers	28.4	0.7	5.7	6.5	nd
7-10mers	23.6	1.1	4.0	4.7	nd
Polymers (>10mers)	62.4	2.4	38.1	15.2	nd

Source: US Department of Agriculture Nutrient Database at: https://ndb.nal.usda.gov/ndb/search/list (Accessed on 16 July 2019)