POSTPRANDIAL LIPEMIC RESPONSES TO VARIOUS SOURCES OF DIETARY FAT IN HEALTHY ADULTS

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Abstract: Postprandial lipemia (PPL) has been identified as an independent risk factor for cardiovascular disease (CVD) and a stronger predictor of CVD risk than fasting triglycerides (TG). However, the effects of various sources of commonly consumed dietary fat on PPL are not well understood. Therefore, the objective of this project was to examine the postprandial TG response to commonly consumed sources of dietary fat in healthy adults. Participants engaged in 4 randomized meal trials separated by at least 1 week. For each meal trial, following a 10-hour overnight fast, participants (n = 10; 5M/5F) consumed a standard high-fat meal (HFM; 13 kcal/kg; 61% fat, 32% CHO) with the fat source derived from either butter (B), virgin unrefined coconut oil (CoO), extra virgin olive oil (OO), or canola oil (CaO). Serial blood draws were collected hourly for 6-hours post-meal to quantify postprandial TG responses. Fasting TG was not different ($p = 0.39$) across trials. Two-way ANOVA revealed a significant time effect ($p < 0.0001$) but no time x meal interaction ($p = 0.56$) or overall meal effect ($p = 0.35$). Meal trials did not differ with regard to TG total ($p = 0.33$) or incremental ($p = 0.14$) area under the curve. Men exhibited significantly higher TG peak ($p < 0.05$) within every meal trial. When data were stratified by sex and the TG response was averaged for each participant, a two-way ANOVA revealed a significant time effect ($p < 0.0001$), time x group interaction ($p = 0.0001$), and group effect ($p = 0.048$). Men had significantly higher TG than women at every time point in the postprandial period ($p < 0.05$). BMI was strongly associated with TG tAUC ($r = 0.79$, $R^2 = 0.63$, $p = 0.006$). In our sample of young healthy adults, acute postprandial TG responses to a single HFM comprised of different dietary fat sources did not significantly differ. Additionally, our findings support the notion that sex and BMI are important determinants of PPL. Future research should determine PPL responses to different fat sources in participants at greater risk for CVD.

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CHAPTER I

INTRODUCTION

Cardiovascular disease (CVD) is a major public health concern and the leading cause of death in the United States (AHA, 2018). Traditional risk factors for CVD include smoking, physical inactivity, poor dietary habits, overweight/obesity, dyslipidemia, diabetes, and hypertension (AHA, 2018). In addition, emerging evidence has given rise to consideration of postprandial changes following single meal consumption as substantially impacting CVD risk, owing partly to the fact that individuals are in a postprandial state for the majority of their day (Hyson *et al.*, 2003). Although research has explored the ways in which traditional risk factors contribute to CVD risk, an incomplete understanding still remains regarding postprandial metabolic changes. Adverse changes that occur in the postprandial period include increases in triglycerides (TG), oxidative stress, inflammation, oxidized low-density lipoprotein, and decreases in high-density lipoprotein (HDL-C) and the vasodilatory response, all of which can negatively influence CVD pathology (Hereika *et al.*, 2014; Hyson *et al.*, 2003; Gower *et al.*, 2011; Kim *et al.*, 2012; Graner *et al., 2006;* Cortes *et* Al.; 2006; Tushuizen *et al.*, 2006).

Postprandial lipemia is the blood lipid response following a meal, whereas postprandial metabolism is the all-encompassing means by which the body physiologically processes the contents of the meal (Hyson *et al.*, 2003). Several studies have shown that an altered or reduced ability to clear TG in the postprandial period (thus, a large post-meal TG response) is associated

with CVD (Lopez-Miranda *et al.*, 2007; Hyson *et al.*, 2003; Boren *et al.*, 2014; Jackson *et al.*, 2012). The connection between postprandial lipemia and CVD has been demonstrated in men with coronary heart disease (CHD) compared to healthy controls and in the sons of men with CHD compared to sons of men without CHD, where both disease-case groups exhibited significantly greater postprandial TG levels (Lopez-Miranda *et al.*, 2007). Similarly, data examined in women have revealed associations between greater postprandial TG and apolipoprotein B-48 (apoB-48) concentrations and CHD (Jackson *et al.*, 2012; Meyer *et al.*, 1996; Bansal *et al.*, 2007). Moreover, in the Women's Health Study and in the Copenhagen City Heart Study, both large prospective cohort studies involving women, non-fasting TG concentrations were significantly associated with increased CVD risk, even after adjustment for various confounding variables (Bansal *et al.*, 2007; Langsted *et al.*, 2011). Generally, when TG accumulate in the postprandial period, they exert adverse effects on the endothelium and promote the exchange of lipids between LDL-C and HDL-C, thus promoting an atherogenic state (Hyson *et al.*, 2003). It has been suggested that the pathophysiology of CVD is driven by the subendothelial penetration and retention of circulating TG-rich lipoproteins (TRL) (Boren *et al.*, 2014; Linton and Fazio, 2003).

Given that high-fat meals (HFMs) classically used to study postprandial lipemia contain >50% fat (Boren *et al.*, 2014; Chan *et al.*, 2013), it is logical that the source of dietary fat can modulate the postprandial TG response. Several studies have found a reduced postprandial lipemic response following meals rich in monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) compared to meals rich in saturated fatty acids (SFA) in both healthy adults and those with characteristics of metabolic syndrome (Masson and Mensink, 2011; Kruse *et al.*, 2015; Jones *et al.*, 2014), in line with classical dietary data showing that certain sources of SFA are generally associated with CVD (Boniface and Tefft, 2002; Mann *et al.*, 1997). Meanwhile, other findings have shown that MUFA and PUFA can induce a greater postprandial

lipemic response compared to SFA (Schwingshackl *et al.*, 2013). Thus, the effects of different dietary fats on postprandial lipemia have been inconclusive to this point. Furthermore, since the effects of a given type of dietary fat on CVD risk can also depend on the source of the fat (e.g. animal- versus plant-based SFA), as has been demonstrated in SFA (de Oliveira Otto *et al.*, 2012), it is reasonable to suspect different postprandial responses based on fat source, even when those foods are comprised of similar fatty acid contents and types. In addition, there is a growing body of evidence suggesting that within different sources of SFA (plant-based, animal-based), various types of animal-based SFA (dairy, meat) may have different effects on CVD risk; specifically, that dairy-based SFA may be protective, while meat-based SFA may be adverse. Considering that postprandial lipemia is an independent risk factor for CVD (Bansal *et al.,* 2007), a better understanding of how various types and sources of dietary fat modify the postprandial TG response would be valuable. Therefore, the primary purpose of this investigation was to determine the effects of different sources of dietary fat as part of a mixed meal on postprandial lipemia in healthy individuals. Specifically, this study compared the postprandial TG response to plant-based SFA (coconut oil), animal-based SFA (butter), olive oil, and canola oil. We hypothesized that: 1) animal-based SFA (B) will exhibit a lesser postprandial lipemic response than plant-based dietary SFA (CoO); 2) plant-based SFA (CoO) will induce a greater postprandial lipemic response compared to CaO-based MUFA, OO-based MUFA, and animal-based dietary SFA (B), but animal-based dietary SFA (B) will induce a lesser postprandial lipemic response compared to the two MUFA sources. 3) OO-based MUFA will induce a greater postprandial lipemic response compared to CaO-based MUFA. The primary outcome in this study is the postprandial lipemic (TG) response. Other classical metabolic indicators (i.e. total cholesterol (TOTAL-C), HDL-C, LDL-C, glucose) are secondary outcomes.

CHAPTER II

LITERATURE REVIEW

Cardiovascular Disease Statistics and Risk Factors

Cardiovascular disease is the leading cause of death in the United States, accounting for 1 out of every 3 deaths and affecting approximately 92.1 million American adults (AHA, 2018). Although certain CVD risk factors, such as age, sex, and genetic makeup, are non-modifiable, several risk factors are modifiable and may, in some cases, be driven by lifestyle choices such as physical inactivity, dietary intake, and overweight/obesity. In 2013-2014, the prevalence of adults in the U.S. that were overweight or obese was 70.7% (CDC, 2013-2014). In 2017, more than 80% of adults did not meet physical activity guidelines including aerobic and muscle-strengthening activities (HHS, 2017). Epidemiological data has identified the connection between diet and CVD, particularly the Western diet and its association with CVD. Western diets are rich in sugar, refined grains, high-fat dairy products, and processed foods and are associated with increased risk for CVD (Hu *et al.*, 2000). On the other hand, a prudent dietary pattern, characterized by consumption of fruits, vegetables, whole grains, nuts and legumes, is associated with a decrease in CVD risk (Hu *et al.*, 2000).

Pathophysiology of Cardiovascular Disease

Cardiovascular disease is a multifactorial pathology involving several overlapping

mechanisms, but is characterized by the buildup of atherosclerotic arterial plaque (Boren *et al.*, 2014; Chan *et al.*, 2013). Atherosclerosis is a type of arteriosclerosis that is initiated by a state of hypercholesterolemia, where apoB-rich cholesterol esters are deposited in the intima and a pro-inflammatory response results. First, lipoproteins containing apoB, namely low-density lipoprotein cholesterol (LDL-C), penetrate and are confined within the intima where they can undergo cleavage, aggregation, and/or oxidation via reactive oxygen species (ROS) (Moore *et al.*, 2013). Oxidized LDL-C activates the endothelium, promoting the expression of adhesion molecules, such as vascular cell adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM). Cytokines, advanced glycation end products (AGEs), and oxidative stress can also activate the endothelium. In the subendothelial space, fat droplets may accumulate in smooth muscle cells. These smooth muscle cells are very diverse and are the major producers of the extracellular matrix within the vasculature. They can act similarly to macrophages and take up lipids, resulting in the formation of cells that resemble foam cells. They can also express adhesion molecules on their surface (VCAM, ICAM) and secrete chemoattractants that initiate the recruitment of monocytes (Doran, Meller, McNamara, 2008). Once the monocytes are captured by adhesion molecules, selectins found on the endothelial surface mediate the rolling of monocytes across the endothelium where they are then activated by chemokines and subsequently arrested by integrins and penetrate the endothelium (Moore *et al.*, 2013). Monocytes, now in the subendothelial space, differentiate into macrophages, stimulated by macrophage colony-stimulating factor (M-CSF), wherein such macrophages engulf oxidized LDL-C found in the endothelial space (Linton and Fazio, 2003). Macrophages play a key role in the adaptive immune response, whereby they serve as antigen-presenting cells. Macrophages also play a key role in the innate immune response, whereby they are activated in an antigen-independent manner (Linton and Fazio, 2003). These macrophages present in atheromatous lesions promote adverse events, such as foam cell formation, and the release of prothrombotic factors, matrix metalloproteinases (MMPs) and cysteine proteases, and pro-inflammatory cytokines (Hansson, 2005; Linton and

Fazio, 2003). Inflammatory markers produced via vascular damage can enter systemic circulation and target hepatic, adipose, and other tissues. Oxidation of LDL-C in the endothelium leads to their detection by pattern recognition receptors (PRR) (Moore *et al.*, 2013). This leads to the uptake of lipoproteins into the endothelium, the accretion of cholesterol esters, and the formation of cholesterol-rich foam cells in the arterial wall.

This atherosclerotic development is soon characterized by proteoglycans binding lipids and expanding further by increasing their disaccharide arms and thus increasing their lipid binding capacity. In addition, oxidative stress and various angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and placental growth factor (PGF), occur throughout the development of atherosclerosis and develop the pathology further. These angiogenic growth factors have been shown to lead to increased macrophage amounts in the endothelium and thus increase plaque formation (Celletti *et al.*, 2001), where smooth muscle cells initiate the production of collagen and the formation of a stiff matrix. These macrophages and smooth muscle cells often turn necrotic within the subendothelial space, and these necrotic fragments stimulate the inflammatory response further, eventually leading to a perturbed intima, enlarged collections of lipids, and ultimately a rigid necrotic core. The smooth muscle cells produce extracellular matrix (ECM) proteins that protect the plaque from rupture by strengthening the fibroatheroma cap; in addition, calcification plays a major role in the thickening of the intima. This fibroatheroma cap covers the necrotic core and is the characteristic plaque formation representative of atherosclerosis. The fibroatheroma cap can be enzymatically degraded by the aforementioned MMPs secreted by smooth muscle cells within the subendothelial space and deteriorated, resulting in a thin cap fibroatheroma (Insull *et al.*, 2009). Because atherosclerotic plaque is a complex structure, no one plaque is the same as the other and each may extend or protrude differently within the vessel wall. The contents within the plaque determine the rigidity of their core – a primarily fibrotic plaque is stiff and hard, a cholesterol-ester rich and

macrophage-rich plaque is soft. Nonetheless, the vulnerability of the plaque is highly dangerous and leads to the increased likelihood of plaque rupture. Eventually, the plaque can rupture, yielding a thrombus, arterial blockage and stenosis (Insull *et al.*, 2009).

Over time, new microvasculature develops within the plaque itself and such events increase the likelihood of plaque rupture (Sluimer *et al.*, 2009). This plaque development is dynamic in activity, meaning that it continuously undergoes changes and has the potential to produce various injurious cardiac events (Scott *et al.*, 2004; Gropper, Smith, & Carr, 2018). Plaque characteristics that are vulnerable to rupture include extensive macrophage infiltration, a thin fibroatheroma cap, reduced quantities of smooth muscle cells, protruding lipid cores, reduced collagen content, and degraded fibroatheroma and matrixes that surround the plaque (Newby *et al.*, 2007). The vulnerability stems from macrophage production of MMPs that degrade the collagen-rich strength of caps surrounding the necrotic cores (Newby *et al.*, 2007). Conversely, macrophages can also mediate the efflux and clearance of apoB containing lipoproteins via the action of the LDL-C receptor. However, the LDL-C receptor is usually less active during states of hypercholesterolemia and foam cell development (Moore *et al.*, 2013). Overall, it is apparent that the pathophysiology of CVD is driven by the subendothelial penetration and retention of circulating lipids. Thus, strategies for improving CVD risk would be logical to target this proximal step in atherosclerosis (Linton and Fazio, 2003).

Dietary Fat, Dietary Guidelines, and Cardiovascular Disease

Typical Western diets are excessive in calories from solid fats, added sugars, refined grains, and sodium. American diets are deficient in the recommended amounts of vitamin- and mineral-rich food sources including fruits, vegetables, and health-promoting fats/oils (Cordain *et al.*, 2005; Carrera-Bastos *et al.*, 2011; Smith, Ng, and Popkin, 2013). Total fat consumption in the U.S. has increased from 57 pounds per person per year in the 1980's to a momentous 78 pounds

per person per year in 2009 (HHS, 2017). Certain sources of dietary fat have been shown to increase LDL-C quantities more than others, including SFA-rich fat sources and MUFA-rich sources (olive oil) when compared to PUFA-rich sources (sunflower oil) (Shepherd *et al.*, 1980; Cortes *et al.*, 2006; Pederson *et al.*, 2000; Kruse *et al.*, 2015). Nonetheless, LDL-C has consistently been associated with CVD (Chapman *et al.*, 2011), and it is clear that fats, whether from animal- or plant-based sources, are a substantial contributor to the American diet and a potential avenue for modulation of CVD risk via their effects on LDL-C.

The 2015 Dietary Guidelines for Americans highlighted the importance of fat in human development and health, and encouraged Americans to become more aware of various types of fats and their health effects (HHS & USDA, 2015). The 2010 Dietary Guidelines for Americans recommendations included limiting solid fats and gave recommendations to use oils, particularly those containing MUFA and PUFA, to replace solid SFA-rich fats when cooking with vegetable oil sources of MUFA and PUFA, and to choose low-fat or fat-free dairy when possible (HHS & USDA, 2010). The recommendation for oils in the Healthy U.S.-Style Eating Pattern at the 2,000-calorie level is 27 g (about 5 teaspoons) per day. The Dietary Guidelines state "oils should replace solid fats rather than being added to the diet". The 2015 Dietary Guidelines for Americans recommendations state that individuals should eat <10% of calories from SFA and still place limits on SFA, but the strict guideline for limiting percent of calories from total fat has been removed (HHS & USDA, 2015).

Within the Scientific Report of the 2015 Dietary Guidelines Advisory Committee's "Needs for Future Research", they stated:

> Examine the effects of saturated fat from different sources, including animal products (e.g. butter, lard), plant (e.g., palm vs. coconut oils), and production systems (e.g. refined deodorized bleached vs. virgin coconut oil) on blood lipids and CVD risk. Rationale:

> Different sources of saturated fat contain different fatty acid profiles and thus, may result in different lipid and metabolic effects. In addition, virgin and refined coconut oils have different effects in animal models, but human data are lacking. (HHS & USDA, 2015, Appendix E-1)

Well-documented, adverse effects associated with intake of dietary SFA include elevated LDL-C (Graner *et al.*, 2006), lower HDL-C (Mattson *et al.*, 1985), insulin resistance (Maron *et al.*, 1991), and obesity (Ward *et al.*, 1994). The effects of SFA on lipids and lipoprotein composition are perhaps the most notable where SFA has been linked to CVD by significantly increasing the concentration of atherogenic LDL-C concentrations (Siri-Tarino *et al.*, 2010). In a 12-year randomized controlled trial (RCT), Turpeinen *et al.* (1979) tested the hypothesis that a diet low in SFA, cholesterol, and high in PUFA ("serum cholesterol lowering diet" or SCL diet), would decrease the incidence of CHD in hospitalized middle-aged men. Researchers found that the incidence of CHD during the SCL diet was half of that of a normal hospital diet and that participants on the SCL diet exhibited significantly lower serum cholesterol values. Similarly, the Oslo Diet-Heart Study enrolled 412 men who had recently experienced a myocardial infarction (MI) and placed the experimental group on a diet low in SFA and cholesterol and high in PUFA. Researchers found that after 5 years of the experimental diet, CHD relapses and fatal and nonfatal MI were all significantly reduced (Leren, 1970). The Nurses' Health Study followed 5,672 women with type 2 diabetes prospectively for 18 years and found that for every 5% increase in energy from SFA, compared to that same energy increase from carbohydrate, there was a 29% greater risk of CVD. Researchers also found that a low PUFA to SFA ratio was associated with an increased risk of CVD (Tanasescu *et al.*, 2004).

However, several recent publications have found null associations between SFA and CVD (Ramsden *et al.*, 2016; de Souza *et al.*, 2015). In a recent meta-analysis and systemic review, researchers found no association among healthy adults between SFA and all-cause

mortality, CHD, CHD mortality, ischemic stroke, or type 2 diabetes (de Souza *et al.*, 2015). Re-evaluation of unpublished data from the Minnesota Coronary Experiment revealed that when linoleic acid was replaced with SFA in the diet, reductions in total cholesterol occur (Ramsden *et al.*, 2016). Another study found no evidence supporting the effects of reduced/modified fat diets in the secondary prevention of CHD, specifically finding that replacing SFA with higher intakes of PUFA was not associated with a decreased risk of CHD (Schwingshackl and Hoffman, 2013). In a prospective study examining the association between SFA from various food sources and incidence of CVD events, researchers found no association between plant-based SFA or animal-based SFA and CVD risk. Researchers also found that after adjustment for various confounding variables, a lower CVD risk was associated with higher consumption of dairy-based SFA and conversely, a higher CVD risk was associated with higher consumption of meat-based SFA (de Oliveira Otto *et al.*, 2012). This study provides possible clarification for why some studies have found an association between SFA and CVD, while others have not. Thus, these findings suggest a potentially incomplete understanding of the relationship between SFA and CVD, as well as a possible overestimation of the benefits of replacing SFA in the diet with various vegetable oils (Ramsden *et al.*, 2016; de Souza *et al.*, 2015). Therefore, more research is still needed to inform dietary recommendations for various sources of dietary fatty acids.

Postprandial Lipemia

Postprandial lipemia is increased circulating TG following a meal, and can occur via increased TG production or reduced catabolism (Boren *et al.*, 2014). Americans on average consume 79 g of fat per day and 4-5 meals per day (Abbot and Byrd-Bredbenner, 2007). The majority of meals, except breakfast, are likely consumed before the body has returned to post-absorptive values and therefore induce summative lipemic increases throughout the day (Boren *et al.*, 2014). Thus, although fasted TG are more commonly assessed in both clinical and research settings, postprandial or non-fasted TG may be more reflective of most individuals' metabolic

state during daily living. An oral fat tolerance test (OFTT) is a non-standardized approach, primarily utilized in research settings, for assessing postprandial lipemia (Chan *et al.*, 2013). An OFTT typically involves administering a test meal consisting of a standard fat source or amount and then monitoring a patient's blood serially for 6-8 hours post-meal.

Postprandial lipemia is thought to promote the previously described atherosclerotic process and this concept is supported by the pro-atherogenic phenomena that have been observed in the context of postprandial lipemia (Hyson *et al*., 2003). Specifically, endothelial function has been shown to be impaired via oxidative stress resulting from postprandial lipemia. Vogel *et al*. (1997) examined the effects of postprandial lipemia on endothelial function by administering a single HFM and a single low-fat meal to 10 healthy participants. The HFM induced significant reductions in flow-mediated dilation (FMD) while the low-fat meal did not, demonstrating that a single HFM can adversely affect endothelial function. High-fat meal-induced endotoxemia has also been a phenomenon observed within the postprandial period contributing to the atherosclerotic process, where HFM intake has induced significant lipopolysaccharide (LPS)-driven inflammation (Cani *et al.*, 2007; Ghanim *et al.*, 2009; Pussinen *et al.*, 2007). Ghanim *et al*. (2009) compared the effects of a western meal (42% kcal from fat (33% SFA), 41% kcal from carbohydrates, 17% kcal from protein), to an American Heart Association (AHA) recommended meal (27% fat, 58% carbohydrates, 15% protein) on postprandial endotoxemia, markers of oxidative stress, and inflammation. The western meal exhibited significant increases in the expression of toll-like receptors, suppressor of cytokine signaling-3, reactive oxygen species (ROS), nuclear factor-KB binding activity, and plasma LPS concentrations, while the AHA meal elicited no change. These results indicate a substantial systemic inflammatory response following consumption of a high-fat Western meal. Moreover, Nappo *et al.* (2002) compared the effects of a HFM and a high-carbohydrate meal on postprandial endothelial activation in healthy subjects and type 2 diabetes patients, with and without vitamin E/ascorbic acid supplementation. Researchers

found that the HFM, without vitamin E/ascorbic acid supplementation, increased concentrations of TNF-α, IL-6, ICAM-1, and VCAM-1 from baseline in healthy subjects; there were also significant associations between changes in postprandial TG and TNF-α, IL-6, and VCAM-1 (Nappo *et al.*, 2002). With regard to oxidative stress, in a study investigating the concentration of oxidized LDL-C during postprandial lipemia in men and women with coronary artery disease (CAD), oxidized LDL-C was significantly elevated during the postprandial period and was associated with the degree of severity of CAD (Graner *et al.*, 2006).

Large epidemiological studies support a strong and clear association between postprandial TG and CVD and that exaggerated postprandial lipemia contributes to CVD risk (Parks, 2001; Nordestgaard *et al.*, 2007; Lindman *et al.*, 2010; Chapman *et al.*, 2011). In fact, postprandial or non-fasting TG measures may be more indicative of cardiovascular risk than fasting blood values (Bansal *et al.*, 2007). In one prospective study, researchers examined the association between fasting serum TG and cardiovascular events over an 11.4-year period in a cohort of ~26,000 women, as well as non-fasting TG concentrations and cardiovascular events in a subset of ~6,000 women, as a secondary analysis of the Women's Health Study data. Prior to adjustment for various confounders, fasting and non-fasting TG were both associated with cardiovascular events. However, in the fully adjusted model, fasting TG were no longer associated with cardiovascular incidents, whereas non-fasting TG remained significantly associated. Specifically, non-fasting TG were associated with cardiovascular incidents in women even after adjustment for age, blood pressure, smoking, use of hormone therapy, total cholesterol, HDL-C, and insulin resistance. Thus, postprandial/non-fasting TG are considered an independent risk factor for CVD, and more strongly associated with CVD than fasting TG (Bansal *et al.*, 2007), hence, their potential to inform CVD development earlier than their fasting counterparts. In another cohort study, as a part of the prospective Copenhagen City Heart Study, researchers examined the relationship between non-fasting TG and ischemic stroke in the broad population, a

total of 13,956 men and women aged 20-93 years. A positive linear association between incidence of ischemic stroke and non-fasting TG levels was found, as well as a 16.7% and 12.2% 10-year risk of ischemic stroke for men and women, respectively, with higher non-fasting TG (Freiberg *et al.*, 2008).

While case-control studies investigating the relationship between postprandial lipemia and CVD are limited, available studies suggest that individuals with CVD exhibit a greater and prolonged post-meal TG response (Chan *et al.*, 2013). Simons *et al*. (1987) found that, after controlling for confounding variables, postprandial apoB-48/apo13100 ratio was still significantly higher in subjects with CAD than in healthy controls, and was a significant predictor of CAD. Moreover, in a case-control study examining the postprandial apoB-48 and TG responses in normolipidemic women compared to matched women with CAD, researchers found that women with CAD exhibited a significantly higher TG response in chylomicron (CM) particles and a greater apoB-48 response than matched controls (Meyer *et al.*, 1996). Patsch *et al.* (1992) found that the overall TG response was higher in males with CAD than in males without CAD, even after adjusting for fasting TG levels. With regard to CVD prediction, Patsch (1992) found that the accuracy of postprandial TG was greater than fasting TG when compared to classically predictive markers, such as HDL-C and total cholesterol, and classified postprandial TG as an independent predictor of CAD in the fully-adjusted multivariate model. Thus, various levels of evidence – that is, mechanistic, epidemiological, and case-control studies – suggest that postprandial lipemia is an important factor with regard to CVD risk.

Influence of Dietary Fat Composition on Postprandial Lipemia

Digestion, Absorption, and Clearance Properties of Fatty Acids

TG are a highly concentrated form of energy that consist of heterogeneous or homogeneous combinations of fatty acids attached to a single glycerol molecule. They are the

major contributor of fat in the diet (exogenous) but can also be synthesized (endogenous) by the body when necessary. After eating, digestion begins in the mouth and stomach with lingual lipase and gastric lipase, respectively. In the stomach, fatty acids within the TG molecule are hydrolyzed at the sn-3 position by gastric lipase, resulting in 1,2-diacylglycerol and fatty acids. Upon entry into the small intestine, TG are highly hydrophobic molecules and require emulsification from bile salts in order for digestive enzymes to have access to the dietary fat droplets. Together with pancreatic lipase, colipase, and bicarbonate, TG are digested to free fatty acids, monoglycerides (MG), and diglycerides (DG). Pancreatic lipase has preferential specificity for the fatty acid at the sn-1 position of the TG molecule, therefore the majority of the remaining MG or DG are 2-monoacylglycerol or 1,2-diacylglycerol. These products are incorporated into micelles, pass an unstirred water layer, and then diffuse into the enterocyte, where they undergo re-esterification into TG molecules. Interestingly, findings also demonstrate that carrier mediated transport may be another mechanism for absorption of the products of TG digestion (Phan and Tso, 2001). Re-esterified TG are packaged into CM with apoB-48 and secreted into the lymphatic system. Short-chain fatty acids (SCFA) and medium-chain fatty acids (MCFA) do not undergo re-esterification or pass through the lymph, but instead, upon absorption into the enterocyte, are secreted directly into circulation where they attach to albumin for transport to the liver. Once CM enter portal circulation, they reach the endothelial surface of adipose and muscle tissue where they are hydrolyzed by lipoprotein lipase (LPL) releasing free fatty acids and MG. These products are either bound to albumin or taken up readily by the muscle or adipose for storage or energy usage. Once CM drop off the majority of their TG, they travel to the liver where they are internalized and degraded/metabolized in the lysosomes. There, *de novo* synthesis from endogenous lipids occurs, where the overflow of TG can also be packaged into very-low density lipoproteins (VLDL-C) and secreted back into circulation. To this effect, VLDL-C then undergo a similar process as CM, arriving at peripheral tissues and interacting with LPL on the surface of the endothelium. Importantly, CM and chylomicron remnants (CMR) compete with VLDL-C for

LPL, but because CM and CMR are larger than VLDL-C molecules, they interact more readily with LPL. As VLDL-C progressively lose their TG, they become intermediate-density lipoprotein cholesterol (IDL-C) and ultimately, LDL-C particles. LDL-C particles are low in TG and richest in cholesterol. Their main function is to deliver cholesterol to peripheral tissues and back to the liver (Chan *et al.*, 2013; Gropper, Smith, & Carr, 2018).

TG partly obtain their role in atherosclerosis via their association with TRL including VLDL-C, VLDL-C remnants, CM, CMR and apo C-III proteins. The subendothelial penetration and retention of lipids related to postprandial lipemia are partly due to the metabolism and activity of CM and CMR. CM are large particles synthesized in the enterocyte and carry mainly exogenous sources of fat to peripheral tissues, especially sizeable amounts of postprandial TG. Although CM and CMR have been known to accumulate in endothelial space throughout the postprandial period (Chapman *et al.*, 2011), CM are too large to breach through the endothelial space. LDL-C and VLDL-C are smaller and more dense and they compete with CM and CMR for clearance therefore, LDL-C and VLDL-C are a larger contributor to the development of atherosclerotic lesions (Boren *et al.*, 2014). As previously stated, once VLDL and CM are hydrolyzed, their smaller, TG-poor and cholesterol-ester-rich remnants, remain in circulation where they can be taken up by macrophages and later form foam cells. Notably, hyperlipemic states have been associated with decreased VLDL clearance and increased VLDL production. By comparison, when CM are taken up by the liver, their TG-rich core is removed and they then become CMR, where they are small enough to pass into the intima (Talayero, Sacks, 2011) but because LDL-C and VLDL-C are smaller, LDL-C and VLDL-C invade the endothelium, dock, and initiate a host of atherogenic metabolic and inflammatory processes (Hyson *et al.*, 2003).

The accumulation of TG in the postprandial period is a complex and dynamic process, owing partly to the concentration of the rate-limiting step for lipid clearance, LPL. Two key proteins present in lipoprotein particles are apoB-48 and apoB-100. ApoB-48 is a component of

exogenous CM and CMR, while apoB-100 is a component of endogenous VLDL-C and LDL-C. The LDL-C receptor recognizes lipoprotein particles based on the apoB protein. Because intestinal and hepatic TRL compete for the same LPL and receptor-mediated uptake, TRL almost always accumulate during the postprandial period – it is the magnitude of increase and time for clearance that is clinically relevant. During this period, lipid exchange and transport is active and shifting, specifically via cholesteryl ester enrichment of TRL by means of exchanges between LDL-C and HDL-C. This exchange can define the state of atherogenicity (Hyson *et al.*, 2003; Gropper, Smith, & Carr, 2018). Consequently, these TRL not only exert their effects via LDL-C, but also via the exchange of TG for cholesterol esters from HDL-C (Chan *et al.*, 2013). Cholesterol-esterase transfer protein (CETP) is a protein responsible for the transfer of cholesteryl esters and TG between lipoproteins, namely, LDL-C and HDL-C. Under normal physiological conditions, CETP facilitates the conversion of HDL-C spherical particle size and lipid content, meaning it transfers cholesteryl esters picked up from peripheral tissues to the liver via scavenger receptor class B type 1 (SR-B1). It promotes cholesterol efflux out of non-hepatic tissues for removal and excretion in bile by the liver (Gropper, Smith, & Carr, 2018).

Evidence for Postprandial Lipemia from Various Fat sources

It is well-established that the amount of dietary fat modulates the postprandial lipemic response and that various fat sources can potentially elicit unique postprandial lipemia responses (Dubois *et al.*, 1998, Thomsen *et al.*, 2003; Tinker *et al.*, 1999). Postprandial lipemia has been investigated in numerous studies across a wide range of populations, amounts of dietary fat, and sources of dietary fat. For example, Dubois *et al*. (1998) found that when normolipidemic individuals ingest various amounts of dietary fat of up to 50 g, postprandial lipemia is directly and positively correlated with the amount of dietary fat ingested. Comparatively, when individuals ingest little to no dietary fat (≤15 g) at a single meal, postprandial lipemia is unaffected. Thomsen *et al.* (2003) observed a substantial postprandial lipemic response in

individuals with type 2 diabetes following meals containing 100 g of butter and 80 g of olive oil, respectively, but observed no significant change in lipemia following the control meal containing 50 g of carbohydrate and 0 energy from fat. Emerson *et al.* (2017) investigated the effects of 3 different meals, one standard HFM, a moderate fat meal, and a biphasic meal, with aims to compare the postprandial TG responses of realistic meals (moderate fat and energy) to a standard HFM used to assess postprandial lipemia. The standard HFM induced a significantly greater postprandial TG response than did the other two meals, indicating that a single large HFM results in a notably different postprandial lipemic response when compared to smaller, less energy-dense meals separated by time intervals. Collectively, these findings suggest that the postprandial lipemic response is largely determined by the amount of dietary fat in the test meal.

Comparatively, the lipemic effects of various fat sources have not been clearly elucidated, although several studies have investigated lipemic effects following ingestion of olive oil, canola oil, and various sources of omega-3 fatty acids. A single meal rich in omega-3 fatty acids, sometimes utilized as an intervention in hypolipidemic interventions, has been shown to elicit a lower postprandial lipemic response compared to a MUFA-rich meal (Tinker *et al.*, 1999). Similarly, olive oil is a key component of the Mediterranean diet that has long been suggested as a protective dietary pattern for CVD and dyslipidemia and has been implicated in hypolipidemic dietary interventions (Covas *et al.*, 2007). The beneficial effects of olive oil can likely be attributed to its predominant MUFA content and to a lesser degree, its polyphenol content (Covas *et al.*, 2007). The effects of olive oil on postprandial lipemia have been seen to be dose-dependent. Weinbrenner *et al.* (2004) observed no effects of 25 mL (24 g) of olive oil on postprandial lipemia, while Fito *et al.* (2008) observed postprandial increases after 40 mL (38 g) of ingested olive oil. Thomsen *et al.* (2003) observed a lower postprandial lipemic response following a meal consisting of 80 g of ingested olive oil when compared to 100 g of ingested butter. Olive oil also induced a more advantageous lipemic response indicated by increased HDL-

C concentrations. However, since the olive oil test meal had a lower amount of total fat (80 g) compared to the butter meal (100 g), these results do not permit a direct comparison of olive oil and butter on postprandial lipemia.

In this context, studies have yielded inconsistent results regarding the lipemic effects of olive oil compared to other fat sources. Mekki *et al.* (2002) recruited 10 healthy young men in a randomized crossover design to evaluate the effects of various common dietary fatty acids in a mixed meal model on postprandial lipemia. Following a 10-hour overnight fast, participants consumed either an energy-free control meal (0 g fat), an animal-based SFA-rich meal with 40 g of fat, an olive oil MUFA-rich meal with 40 g of fat, or a sunflower oil PUFA-rich meal with 40 g of fat. Besides the fat source, the meal was identical across trials and consisted of French bread, pasta, tomato sauce, no-fat yogurt, and either the test fat or no fat (control). Blood samples were taken at baseline and serially every hour for 7-hours after the meal to assess the postprandial TG response. Mekki *et al*. found that, when compared to SFA-rich meals, olive oil induced a greater postprandial lipemic response, but a comparable postprandial response to PUFA-rich meals, concluding that butter resulted in lower postprandial lipemia than olive (MUFA) and sunflower oil (PUFA) rich meals. The lower lipemic response observed in some studies following ingestion of dairy-based SFA-rich meals may be due to slow emulsification of butter-fat accompanied by delayed gastric emptying (Mekki *et al.*, 2002, Tholstrup *et al.*, 2001). Owing partly to the fact that the process of fat digestion and emulsification produces oil-in-water emulsified lipids and considering that the dairy-based SFA-rich butter is a water-in-oil emulsion, it is not the most appropriate substrate for gastric and intestinal lipases (Gropper, Smith, & Carr, 2018). The process of TG digestion begins briefly in the mouth but continues in the stomach where gastric lipase preferentially hydrolyzes the TG at the sn-3 position, releasing a free fatty acid and 1,2-diacylglycerol. Once in the small intestine, pancreatic lipase favors the hydrolysis of the TG molecule at the sn-1 position, secondarily at the sn-3 position, once again reinforcing the notion

of a preferential digestion process. Lingual and gastric lipases favor MCFA and SCFA, therefore the process of fat digestion confers different effects depending on the length of the fatty acid chain, the type of fatty acid, and the position of the fatty acid. The end-products of TG digestion are therefore mainly free fatty acids and 2-monoacylglycerols. Within the enterocyte, preferential positioning of SCFA and MCFA at the sn-1 and sn-3 position displaces long-chain saturated fatty acids (LCSFA), resulting in less access to LCSFA (Gropper, Smith, & Carr, 2018). Moreover, ~20% butter-fat is SCFA and MCFA, potentially explaining the reduction in the size and amount of CM in the postprandial period observed by Mekki *et al*. (2002). One could speculate that because ~20% of butter-fat is SCFA and MCFA, this would lead to greater overall clearance and lower lipemia owing to the fact that SCFA and MCFA are immediately transported into portal circulation. As observed by Mekki *et al*. (2002), Bonham *et al*. (2013), and Tholstrup *et al*. (2001), it is reasonable to speculate that reduced endovascular lipolysis may be one mechanism by which SFA may elicit a lower and slower postprandial lipemia when compared to other dietary fatty acids.

Another study aimed to compare the effects of palmitic SFA-rich sources of fat from either animal (lard) or plant (palm olein) sources to oleic MUFA-rich dietary fat (virgin olive oil) as part of a mixed meal on postprandial TG, glucose, insulin and adipokines (Teng *et al.*, 2011). The test meal consisted of mashed potatoes, baked beans, skim milk, orange juice, and the test fat that provided 60% of total kcal (50 g of fat from virgin olive oil, palm olein, or lard). Researchers found that the palmitic SFA-rich lard elicited a significantly lower TG response than the oleic MUFA-rich olive oil and palmitic SFA-rich palm olein. It is important to note that Albia *et al.* (1999) found that CM enter portal circulation more rapidly and are metabolized faster following ingestion of olive oil or olive oil-rich meals compared to other sources of dietary fatty acids, therefore adding support to the notion that, despite rises in postprandial lipemia following

ingestion olive oil, postprandial rises in TG may be handled more efficiently when compared to other sources of dietary fatty acids.

Another major source of MUFA in the diet is canola oil. Although data studying acute postprandial lipemia following consumption of canola oil is limited, Nielsen *et al.* (2007) observed the acute postprandial effects of a short-term diet rich in either rapeseed oil (essentially canola oil), olive oil, or sunflower oil, challenged with consumption of a single rapeseed oil-rich meal. They observed that the postprandial TG concentrations were highest following the olive oil diet compared with the rapeseed oil and sunflower oil diet (Nielsen *et al.*, 2007). In another study specifically investigating acute postprandial lipemia (Calabrese *et al.*, 1999), participants consumed either 71 g of medium-chain triglycerides (MCT) oil, representative of the predominating fatty acid found in coconut oil, or canola oil and the TG response was observed for 5 hours. The authors found that plasma TG concentrations increased 47% from baseline after the canola oil ingestion, while they increased only 15% from baseline following MCT oil ingestion. Considering that the dominant fatty acid present in canola oil is oleic acid, studies investigating the postprandial effects of oleic acid can be comparable to the effects of canola oil. Sanders *et al.* (2001) found that when healthy participants consumed HFMs consisting of MCT, palmitate, stearate, elaidate, or oleic acid, TG responses were greater after the oleic acid, elaidate, and palmitate meals than the stearate and MCT meals. Tholstrup *et al.* (2001) also observed a similar postprandial lipemic response in which meals rich in unsaturated fatty acids, one of which being oleic acid, resulted in a greater lipemic response than did LCSFAs.

Data generally suggest a lower postprandial TG response following SFA-rich meals compared to other types of dietary fat. As mentioned previously, Mekki *et al.* (2002) had ten healthy young men consume a standard meal consisting of 40 g of either animal-based SFA (butter), MUFA (olive oil), PUFA (sunflower oil), or 0 g fat (control). The SFA meal elicited a lower postprandial response, for both serum TG and CM, than the two unsaturated fat oils and the

two unsaturated oils did not differ in their effects (Mekki *et al.*, 2002). These results were in agreement with data obtained from Tholstrup *et al.* (2001) who found that the intake of LCSFA, both stearic and palmitic acid, resulted in a lower postprandial lipemic response when compared to the unsaturated fatty acids. Furthermore, Tholstrup (2001) observed that the LCSFA led to a lower postprandial lipemic response than did the MCFA, myristic acid. Finally, the authors also observed that the LCSFA took longer to return to post-absorptive values than did the unsaturated fatty acids, but this did not result in higher concentrations of CETP. Moreover, in a case-control study by Bonham *et al*. (2013), 9 healthy males and 11 males with metabolic syndrome consumed two HFMs – one from dairy-based foods and one from vegetable oil-based foods. Postprandial lipemic responses were significantly lower after the SFA-rich dairy-based foods when compared to the vegetable oil-based foods in all participants. The authors speculate that these findings could be due to the higher concentration of short and medium chain fatty acids present in the dairy-based HFM and/or the greater bioavailability and absorption of calcium in the dairy-based HFM leading to the formation of insoluble calcium soaps with fatty acids and greater fat excretion.

Other studies have shown opposing effects of SFA, including higher postprandial TG responses when compared to other dietary fatty acids (Micha *et al.*, 2010). One study fed healthy young men three meals in a crossover design separated by 1 week: a control meal consisting of 50 g of carbohydrate and 0 g fat, the control meal plus 100 g of animal-based SFA (butter), and the control meal plus 80 g of MUFA-rich olive oil (Thomsen *et al.*, 1999). Researchers found an elevated postprandial lipemic response following the SFA-containing meal, characterized by elevations in TG and prolonged accumulation of CM. On the other hand, they found only small increases in TG and nearly no increases in CM following the MUFA-rich olive oil meal. Rivellese *et al.* (2008) found no significant difference in lipemic responses between a 3-week MUFA-rich diet and SFA-rich diet when challenged with a standard fat-rich meal consisting of a potato pie with potato, whole milk, egg, cheese, ham, and butter (57% total fat, 34% SFA),

although the MUFA-rich diet reduced the amount of VLDL-C in circulation and increased the activity of LPL and hormone-sensitive lipase (HSL) following the standard fat-rich meal. In another study conducted with overweight men who had an increased risk for metabolic syndrome, participants consumed 50 g of either animal-based SFA (butter) or PUFA (margarine, sunflower oil) in a mixed meal (51% fat for the butter meal, 53% fat for the margarine meal). The authors found that TG responses did not significantly differ between meals (Masson and Mensink, 2011). Thus, while there are numerous studies demonstrating that HFMs rich in SFA tend to elicit a lower postprandial TG response compared to meals rich in MUFA and PUFA, there are also studies suggesting no difference or a greater TG response following SFA intake.

The inconsistencies observed in the literature regarding the effects of different fat sources on postprandial lipemia can likely be attributed to a combination of different factors, including study design (testing one or multiple fat sources, crossover and washout periods, physical activity and lifestyle controls), meal composition, amount of fat, dietary intake leading up to the OFTT, study sample, and the type/source of dietary fat. Many of the studies utilizing an OFTT or an acute postprandial design have been conducted in individuals with metabolic dysfunction, obesity, type 2 diabetes, or various comorbidities. Similarly, a large number of studies have used a standard amount of fat with or without incorporation into a mixed meal, disregarding disparities in body weight, composition, and effects of various components in meals (carbohydrates, protein, sugar). Body weight, body composition, and the composition of meals have all been shown to independently affect postprandial lipemia (Hyson *et al.*, 2003).

Although there has been a great deal of research examining the effects of long-term consumption of SFA, there is a very limited amount of research on the acute effects of SFA as a part of a mixed meal, and more specifically, the comparison of various sources of SFA to each other. Much of the research has focused on either animal-based SFA (primarily from dairy) or plant-based SFA independently (Malhorta *et al.*, 2017). An exception is a study conducted by

Teng *et al*. (2011), which compared the effects of MUFA-rich olive oil, animal-based SFA-rich lard, and plant-based SFA-rich palm olein, on the postprandial lipemic response. The authors found that the animal-based SFA-rich lard elicited a significantly lower lipemic response than the plant-based SFA-rich palm olein and the MUFA-rich olive oil. Similarly, a more recent study published in 2019 aimed to investigate the effect of animal-based SFA (butter), plant-based SFA (coconut oil), and animal-based SFA (lard) on postprandial lipemia in healthy adults. In a randomized single-blind crossover design, sixteen healthy adults (8 M/8 F) were recruited and consumed a mixed meal consisting of biscuits and the dietary fat. The test meals contained ~660 total kcal, of which 53-55% of kcal was derived from fat. Blood samples were taken at baseline and 2, 3, 4, and 6 hours post-meal. The postprandial lipemic response was ~60% lower after the coconut oil meal when compared to the butter meal and the lard meal and no difference was observed between the butter and lard meal, concluding that plant-based SFA resulted in lower postprandial lipemia than animal-based SFA (Panth *et al.*, 2019). These results by Panth (2019) contrast those found by Teng (2011); thus, the impact of different sources of commonly consumed SFA as part of a mixed meal on the postprandial lipemic response remains unknown and results of existing studies are contradictory. Further, little is known regarding the lipemic effects of plant- and animal-based SFA compared to commonly consumed sources of unsaturated fat (e.g. olive oil, canola oil). Given the rising popularity of certain plant-based SFA (e.g. coconut oil), and the clinical relevance of the postprandial response to CVD, assessment of how these different fat sources modulate postprandial lipemia would be practical and valuable.

Therefore, the purpose of this study was to compare the lipemic effects of four commonly consumed dietary fat sources as a part of a mixed meal: butter (B) (animal-based SFA), coconut oil (CoO) (plant-based SFA), canola oil (CaO) (MUFA), and olive oil (OO) (MUFA). We hypothesize that: 1) animal-based SFA (B) will exhibit a lesser postprandial lipemic response than plant-based dietary SFA (CoO); 2) plant-based SFA (CoO) will induce a greater postprandial

lipemic response compared to CaO-based MUFA, OO-based MUFA, and animal-based dietary SFA (B), but animal-based dietary SFA (B) will induce a lesser postprandial lipemic response compared to the two MUFA sources. 3) OO-based MUFA will induce a greater postprandial lipemic response compared to CaO-based MUFA. The primary outcome in this study is the postprandial lipemic (TG) response. Other classical metabolic indicators (i.e. total cholesterol (TOTAL-C), HDL-C, LDL-C, glucose) are secondary outcomes.

CHAPTER III

METHODOLOGY

Participants

Ten individuals (5 men, 5 women) participated in the present study and were recruited via online survey, email, or flyer from the Oklahoma State University campus. Inclusion criteria were age 18-40 years, no evidence of dietary intolerances that precluded consumption of the test meals, no chronic disease, and not taking any lipid or blood pressure medications. The study protocol was approved by the Institutional Review Board at Oklahoma State University (HE-17-77) and all participants provided verbal and written consent prior to participating in the study.

Overall Study Design

Participants engaged in one initial assessment and four randomized meal trials. The initial assessment consisted of paperwork and anthropometric data measurements. Participants were also administered various lifestyle control instructions during the initial assessment. Meal trials began approximately 1 week after the initial assessment. Each meal trial was separated by a washout period of 1-3 weeks. The sequence in which a participant consumed the 4 test meals was randomized. Within each meal trial, participants arrived in the laboratory 10-hours fasted, a baseline blood draw was taken, they consumed the test meal, and blood draws were taken every hour for 6-hours post-meal to determine the postprandial TG response.

Initial Assessment

The initial assessment, conducted approximately 1 week prior to the first meal session, entailed detailed copies of instructions for participants to follow, completion of written informed consent, a medical history questionnaire, the international physical activity questionnaire (IPAQ), and anthropometric evaluations. Height was measured via stadiometer (Seca 213 portable stadiometer; Seca GmbH; Hamburg, Germany). Weight was assessed using a combination scale and bioelectrical impedance analyzer (Seca mBCA 514; Seca GmbH; Hamburg, Germany). Blood pressure was measured using an automatic blood pressure cuff (Omron 5 Series BP742N; Omron; Kyoto, Japan). Height, weight, and blood pressure were measured twice and the average of the two measures was recorded.

Lifestyle controls were assigned and all participants were instructed regarding compliance. Lifestyle controls consisted of a 3-day food record, in which participants recorded their dietary intake for the 3 days prior to their first meal assessment; participants then were asked to replicate their first 3-day food record for the remaining 3 meal assessments. Accelerometers (wGT3X-BT, Actigraph; Pensacola, FL, USA) were attached to each participant's non-dominant wrist and recorded their physical activity for at least 48 hours prior to each assessment. In addition, participants were asked to refrain from planned exercise for the 48 hours prior to each assessment. Participants were given a 210-kcal snack, consisting of commercial peanut butter crackers (Snyder's-Lance, Inc.; Charlotte, NC), to consume the evening before each assessment, after which the 10-hour fast began. Participants were given a typed copy of all detailed instructions and lifestyle controls.

Meal Trials

After a 10-hour overnight fast, participants arrived in the laboratory on the morning of each assessment. Sessions began between 0600-0800 hours, depending on the scheduling availability

of each participant. An indwelling 24-gauge safelet catheter (Exel International; Redondo Beach, CA) was inserted into a forearm vein and a slow infusion (~1 drip/s) of 0.9% NaCl solution was initiated. Once the catheter was set, a baseline blood draw was collected. First, a 3 mL syringe (BD; Franklin Lakes, NJ, USA) was used to clear the line of saline followed by a 5 mL syringe (BD; Franklin Lakes, NJ, USA) to take the whole blood sample. Whole blood samples were collected for the assessment of metabolic outcomes: TG, glucose, LDL-C, HDL-C, and TOTAL-C. Metabolic outcomes were determined by a Cholestech LDX analyzer (Alere Inc.; Waltham, MA, USA). For each individual blood draw, a few drops of whole blood were drawn into a capillary tube and plunged into a Cholestech LDX Lipid+Glu cassette (Alere Inc.; Waltham, MA, USA). The cassette was inserted into the Cholestech LDX analyzer and processed. The CV for TG assessment via the Cholestech LDX system is approximately 2-4%. Following the baseline blood draw, participants consumed the test meal within 20 minutes. Water was available for participant consumption *ad libitum* during the meal and throughout the postprandial period. Participants remained in the laboratory for 6 hours following consumption of the test meal. The 6-hour time period began after the last bite of the test meal. Additional blood draws were performed every hour for the 6 hours after consumption of the test meal.

Test Meals

The test meal consisted of pasta sauce, whole-wheat spaghetti noodles, French bread, yellow onion, green bell pepper, sea salt, black pepper, and the specific fat source being tested. Each meal contained either MUFA-based CaO (Great Value, Canola Oil), MUFA-based extra virgin OO (Great Value, Extra Virgin Olive Oil), SFA-based virgin unrefined CoO (Organic Great Value, Unrefined Virgin Coconut Oil, expeller pressed), or SFA-based grass-fed B (Kerrygold, Grass-fed Pure Irish Butter, unsalted). The test meal contained 61% of total kcal from fat, 7% from protein, and 32% from carbohydrate (CHO), respectively. Each participant consumed a serving of the test meal that was relative to his or her body mass (13 kcal/kg body mass). The

amount of meal consumed was designed to resemble a typical serving at a restaurant or social event (1-2 servings). For each assessment, the test meal was prepared independently 1-2 days prior to the assessment. To prepare each meal, the test fat was added to a small saucepan and heated over medium heat for 2-minutes. Onion and bell pepper were diced finely and sautéed over medium heat in a large sauce pan for 3 minutes. The pasta sauce was added to the saucepan and brought to a boil, after which the heat was reduced, the saucepan was covered, and the mixture cooked for 7 minutes until the internal temperature reached 165°F. Once the pasta sauce mixture was finished cooking, it was removed from the heat, cooled for 20 minutes, labeled, and stored in a BPA-free food storage container at 0°F until needed for each assessment. The night before each assessment, the pasta sauce was thawed at 36°F overnight. On the morning of each assessment, the noodles were prepared separately by bringing 4 cups of water to a boil in a medium saucepan, after which the raw noodles were added, cooked uncovered for 9 minutes, and strained. The pasta sauce was reheated in a small saucepan until the internal temperature reached 165°F. The pasta sauce and noodles were combined in a small serving bowl and the French bread was served on the side. All ingredients were weighed (g) using a digital food scale (**Table 1**).

Statistical Analyses

An *a priori* sample size estimation, based on previous published studies (Mekki *et al.,* 2002), suggested that 10 participants would need to be recruited to detect statistically significant differences in the postprandial TG response ($\alpha = 0.05$). Thus, we recruited 10 participants in order to have sufficient power to detect differences in postprandial lipemia.

All data were assessed for normality via Shapiro-Wilk formal normality test and analysis of frequency distribution. The trapezoid method was used to calculate tAUC and incremental area under the curve (iAUC). Within each meal trial, tAUC, iAUC, peak value, and time to peak value were determined for each of the metabolic markers. These postprandial metabolic outcomes were

compared across trials using a one-way analysis of variance (ANOVA) with Holm-Sidak adjustment for multiple comparisons. Time-course changes and sex-based differences in metabolic markers in the postprandial period were determined via two-way (group x time) repeated measures ANOVA with a Tukey's adjustment for multiple comparisons.

Differences with regard to participant characteristics were compared by sex via two-tailed paired *t*-test. Pearson's two-tailed correlation analysis was performed to assess the association between participant BMI and TG tAUC (averaged across meal trials).

A type 1 error rate of 0.05 was used in all analyses for the determination of statistically significant differences. Statistical analyses were conducted using GraphPad Prism statistical software (Version 7; GraphPad Software, Inc; La Jolla, CA).

CHAPTER IV

RESULTS

Participant characteristics and pre-meal physical activity

Participant characteristics are presented in **Table 2**. Ten individuals participated in the present study (5 M/5 F; age: 23.8 ± 1.3 years; BMI: 25.5 ± 7.2 kg/m^2). Based on body mass index (BMI), six participants (1 M/5 F) were healthy weight (18.5-24.9 kg/m^2), one participant (1 M) was overweight (25-29.9 kg/m^2), and three participants (3 M) were obese (>30 kg/m^2). One participant reported with fasting TG > 150 mg/dL on two occasions. Men were significantly older (mean difference: 1.2 years; $p = 0.03$) and had greater weight (mean difference: 36.2 kg; $p = 0.01$) and BMI (mean difference: 9.6 kg/m^2; $p = 0.02$) compared to women. Men reported with higher fasting LDL-C concentrations when compared to women (mean difference: 41.8 mg/dL; $p = 0.02$), but there were no differences in fasting TG ($p = 0.21$), glucose ($p = 0.96$), TOTAL-C ($p = 0.44$), or HDL-C ($p = 0.30$) between men and women. Additionally, fasting TG ($p = 0.39$), glucose ($p = 0.13$), TOTAL-C ($p = 0.07$), LDL-C ($p = 0.86$), and HDL-C ($p = 0.11$) were not different across meal trials. Physical activity, measured as moderate-vigorous physical activity (MVPA) and steps/day, was not different across meal trials ($p = 0.84$ and $p = 0.69$, respectively) and there was not main effect by meal trial ($p = 0.69$; $p = 0.90$), sex ($p = 0.68$; $p = 0.51$), or meal x sex interaction ($p = 0.20$; $p = 0.67$) (**Figure 1**).

Postprandial metabolic outcomes were similar across meal trials

Metabolic outcomes are presented in **Table 3** and **Figure 2**. Two-way ANOVA of TG revealed a significant time effect ($p < 0.0001$) but no time x meal interaction ($p = 0.56$) or overall meal effect ($p = 0.35$). One-way ANOVA revealed that TG peak ($p = 0.36$) and TG time to peak ($p = 0.23$) were not different across meal trials. Meal trials did not differ with regard to TG tAUC ($p = 0.33$) or TG iAUC ($p = 0.14$). Two-way ANOVA of glucose revealed no time effect ($p = 0.27$), meal effect ($p = 0.64$), or time x meal interaction ($p = 0.63$). Glucose peak ($p = 0.76$) and glucose time to peak ($p = 0.48$) were not different across meal trials. Meal trials did not differ with regard to glucose tAUC ($p = 0.60$) or iAUC ($p = 0.26$). Two-way ANOVA of metabolic load index (MLI; calculated as TG + glucose) revealed a time effect ($p < 0.0001$) but no meal effect ($p = 0.08$) or time x meal interaction ($p = 0.77$). MLI peak ($p = 0.24$) and time to peak ($p = 0.64$) were not different across meal trials. Meal trials did not differ with regard to MLI tAUC ($p = 0.12$) or MLI iAUC ($p = 0.08$). Two-way ANOVA of LDL-C revealed no time effect ($p = 0.27$), meal effect ($p = 0.83$), or time x meal interaction ($p = 0.72$). One-way ANOVA revealed that LDL-C peak ($p = 0.66$) and time to peak ($p = 0.59$) were not different across meal trials. Meal trials did not differ with regard to LDL-C tAUC ($p = 0.62$) or iAUC ($p = 0.72$). HDL-C results did not reveal a time effect ($p = 0.62$), meal effect ($p = 0.2$), or time x meal interaction ($p = 0.42$). One-way ANOVA revealed that HDL-C peak ($p = 0.19$) and time to peak ($p = 0.52$) were not different across meal trials. Meal trials did not differ with regard to HDL-C tAUC ($p = 0.23$) or iAUC ($p = 0.16$). Two-way ANOVA of TOTAL-C revealed no time effect ($p = 0.29$), meal effect ($p = 0.07$), or time x meal interaction ($p = 0.82$). One-way ANOVA revealed that TOTAL-C peak ($p = 0.12$) and TOTAL-C time to peak ($p = 0.09$) were not different across meal trials. Meal trials did not differ with regard to TOTAL-C tAUC ($p = 0.11$) or iAUC ($p = 0.37$).

Postprandial lipemic responses were different between men and women

When data were stratified by sex, a two-way ANOVA of TG revealed a significant time effect (men, $p < 0.0001$; women, $p = 0.0002$), but no time x meal interaction (men, $p = 0.20$; women, $p = 0.21$) or overall meal effect (men, $p = 0.53$; women, $p = 0.48$). When averaged across meal trials, men had a significantly higher TG peak ($p = 0.03$) when compared to women, but there was no difference in TG time to peak between men and women ($p = 0.87$). Further, men exhibited significantly higher TG peak ($p < 0.05$) within every meal trial (Mean sex difference: B, 131.6 mg/dL, $p = 0.0005$; CoO, 96 mg/dL, $p = 0.006$; OO, 93.4 mg/dL, $p = 0.007$; CaO, 108.8 mg/dL, $p = 0.002$) (**Figure 3**). When data were stratified by sex and the TG response was averaged for each participant, a two-way ANOVA revealed a significant time effect ($p < 0.0001$), time x group interaction ($p = 0.0001$), and group effect ($p = 0.048$) (**Figure 4**). In *post hoc* pairwise testing, men had significantly higher TG than women at every time point in the postprandial period ($p < 0.05$). Postprandial TG responses in men and women within each meal trial are presented in **Figure 5**. When data were stratified by sex for men and women, there was a significant time effect ($p < 0.0001$, $p = 0.0002$), but no time x group interaction ($p = 0.19$, $p = 0.21$) or overall group effect ($p = 0.53$, $p = 0.47$), respectively **(Figure 6)**. When data were stratified by sex for the B and OO meal trial, a two-way ANOVA of TG revealed a significant time effect (p's < 0.0001) and time x group interaction ($p = 0.001$ and $p = 0.002$, respectively), but no overall group effect ($p = 0.057$ and $p = 0.11$, respectively). When data were stratified by sex for the CoO and CaO meal trial, a two-way ANOVA of TG revealed a significant time effect ($p < 0.0001$, $p = 0.0015$), time x group interaction ($p < 0.0001$, $p = 0.04$), and overall group effect ($p = 0.02$, $p = 0.047$). In *post-hoc* pairwise testing, men had significantly higher TG at baseline, 1, 2, 3, 4, 5, and 6 hours post-meal for the CoO meal trial and at 2, 3, and 4 hours post-meal for the CaO meal trial. Although there was a non-significant group effect for the B and OO meal, in *post-hoc* pairwise testing men had significantly higher TG at 1, 2, 3, 4, 5, and 6 hours post-meal for the B and OO

meal trial. When Pearson's two-tailed correlation was performed, BMI was strongly associated with TG tAUC ($r = 0.79$, $R^2 = 0.63$, $p = 0.006$) (**Figure 7**).

CHAPTER V

DISCUSSION

Postprandial Triglyceride Responses Between Meals

The present study compared the effects of a high-fat mixed meal rich in butter, coconut oil, olive oil, or canola oil on the postprandial metabolic response in healthy adults. Peak postprandial TG concentrations were observed at 2-4 hours post-meal (mean peak across meals: 140.6 mg/dL) and suggest that the HFM used in the present study induced a robust postprandial response. In our sample of young healthy volunteers, consumption of a mixed HFM containing various sources of commonly consumed dietary fat did not result in different postprandial TG responses. Therefore, counter to our hypotheses, the results of this study do not support the notion that various sources of dietary fat result in markedly different postprandial lipemic responses. As postprandial lipemia has been identified as an independent and clinically relevant risk factor for CVD, these results advance understanding with regard to the effects of different dietary fats on cardiometabolic health.

Our finding of similar postprandial lipemic responses across meal trials agrees with those of several previous studies. Rivellese *et al.* (2008) examined the effects of a short-term dietary intervention consisting of a 3-week MUFA-rich diet or SFA-rich diet after which a postprandial challenge was conducted to determine the postprandial lipemic response. In agreement with our findings, the researchers found no significant difference in lipemic responses between the MUFA-rich diet or SFA-rich diet, although this study was comparing the effects of diet rather than a single meal. Another study examined the lipemic effects of a mixed breakfast meal with the fat derived from almonds (MUFA) or cream cheese (dairy-based SFA) in overweight/obese

pregnant women and found no significant difference in the postprandial TG response between the two meal trials (Lesser *et al*., 2019). The meals were isocaloric and contained approximately 42% fat, 12% protein, and 46% CHO. The cream cheese meal contained 24% of kcal from SFA and the almond meal contained 4% of kcal from SFA. These results are in agreement with our findings, as the postprandial TG response to mixed meals rich in SFA or MUFA did not differ. Notably, the test meals utilized in the above studies were mixed meals, containing a heterogeneous mixture of macro- and micronutrients. Likewise, the HFM meal used in the present study contained moderate amounts of CHO (32% of total kcal) derived from fiber-rich whole grains, French bread, and vegetables. As part of a mixed meal, fiber has been shown to blunt the postprandial lipemic response by interfering with lipid absorption and digestion via impairment of proper emulsification of lipids in the gastrointestinal tract (Kristensen *et al*., 2013). In support of this concept, Lesser *et al.* (2019) utilized a mixed meal consisting of 46% of calories derived from CHO and found no differences between test meals. The almond test meal contained 7 g more fiber when compared to the cream cheese test meal, therefore the lack of detectable differences between meals may have been a result of the modifying effect of fiber on postprandial lipemia. Kristensen *et al*. (2013) found that when participants consumed a mixed meal with added fiber from flaxseed, the mean TG response was 18% lower when compared to the low-fiber control, reaffirming the notion that fiber interferes with the postprandial handling of lipids. Consequently, in the present study, the presence of fiber and other nutrients besides fat in the test meal may have weakened our ability to detect differences between meals, given the buffering effect that fiber has on the magnitude of postprandial lipemia.

By contrast, some previous studies have found differences in postprandial lipemia based on source of dietary fat. Sun *et al.* (2018) examined the effects of mixed meals containing low (basmati rice) or high (jasmine rice) glycemic index (GI) CHO and three different types of dietary fat sources (B, OO, grapeseed oil) on the postprandial metabolic response in healthy adults.

Meals were isocaloric and contained 50 g of CHO and 40 g of fat. The postprandial response was measured at baseline and 15, 30, 45, 60, 90, 120, 150, 180, 210, and 240 minutes post-meal. The TG iAUC was significantly lower following the B (SFA) and grapeseed (PUFA) meals when compared to the OO (MUFA) meal, regardless of GI. These results contrast the findings of our present study that found a similar postprandial TG response when comparing the B (SFA) meal with the OO (MUFA) meal.

Similarly, Mekki *et al.* (2002) recruited 10 healthy young men in a randomized cross-over design to assess the effects of various dietary fatty acids in a mixed HFM on postprandial lipemia. Following a 10-hour overnight fast, participants consumed an energy-free control meal (0 g fat), a B (SFA-rich) meal, an OO (MUFA-rich) meal, or a sunflower oil (PUFA-rich) meal. The meal was isocaloric, contained the same amount of fat (40 g) across meal trials, and consisted of French bread, pasta, tomato sauce, non-fat yogurt, and either the test fat or no fat (control) – a test meal similar to that used in the present study. Blood samples were taken at baseline and serially every hour for 7 hours after the meal to assess the postprandial TG response. The authors found that, when compared to the B meal, OO induced a greater postprandial lipemic response, but a comparable postprandial response to the sunflower oil meal, concluding that B resulted in lower postprandial lipemia than the OO and sunflower oil meals. These results disagree with our results but are in line with Sun *et al.* (2018). Mekki (2002) found that the size of circulating CM were consistently lower after the meal rich in B than those detected after the meals rich in vegetable oils (OO or sunflower oil). Although not an explanation as to why these authors found differences between various dietary fats and the present study did not, the lower TG response in the B trial could have been a result of greater or faster lipolysis of CM containing fatty acids from B or a reduced overall size of secreted CM due to the calcium present in B, contributing to the formation of calcium-soap complexes. For our present study, examining the size of circulating CM and concentrations of either intestinally derived apoB-48 present in CM and/or endogenous

apoB-100 present in LDL-C and VLDL-C may have yielded detectable differences between meal trials. Additionally, Mekki *et al*. (2002) did not standardize the test meals to body weight and used a homogeneous sample consisting of only men. These factors may also partially explain the discordant findings between our study and those of Mekki *et al*. (2002).

In contrast to Teng *et al.* (2011), Sun *et al.* (2018), Mekki *et al.* (2002), and our present study, Thomsen *et al.* (2003) observed a lower postprandial lipemic response following a meal consisting of 80 g of ingested OO when compared to 100 g of ingested B. However, since the OO test meal had a lower amount of total fat (80 g) compared to the B meal (100 g), these test meals were not a uniform comparison of the independent effects of OO and B on postprandial lipemia. In another study investigating acute postprandial lipemia (Calabrese *et al.*, 1999), participants consumed either 71 g of MCT oil, representative of the predominating fatty acid found in CoO, or CaO (MUFA), and TG were measured at baseline and serially for 5-hours post-meal. The authors found that plasma TG concentrations increased 47% from baseline after the CaO ingestion, while they increased only 15% from baseline following MCT oil ingestion. Notably, only males were included in this study sample and the test meal was not standardized to body weight, nor was it a mixed meal.

Despite several studies comparing the effects of SFA with MUFA or PUFA, there are very few studies examining the acute effects of various sources of SFA (plant- and animal-based) on postprandial lipemia. Teng *et al.* (2011) compared the effects of animal-based SFA (lard) and plant-based SFA (palm olein) sources to oleic MUFA-rich dietary fat (virgin OO) as part of a mixed meal on postprandial TG. The test meal consisted of mashed potatoes, baked beans, skim milk, and orange juice. The test fat provided 60% of total kcal (50 g). Researchers found that the lard (animal-based SFA) elicited a significantly lower TG response than the OO and palm olein (plant-based SFA). On the other hand, a recent study by Panth *et al.* (2019) examined the effects of various sources of SFA on the postprandial lipemic response in healthy adults. The test meal

consisted of biscuits and 40 g of B, CoO, or lard, and the postprandial metabolic response was measured at baseline, 2, 3, 4, and 6 hours post-meal. The meals contained 660-667 total kcal and 53-55% of kcal from fat. Researchers found that the postprandial lipemic response was ~60% lower after the CoO meal (plant-based SFA) when compared to the B meal (animal-based SFA) and the lard meal (animal-based SFA). No difference was observed between the B and lard meal for postprandial lipemia. These findings disagree with Teng *et al*. (2011), who found that plant-based SFA (palm olein) elicited a greater postprandial lipemic response when compared to animal-based SFA (lard). Teng *et al*. (2011) found that animal-based SFA (lard) resulted in lower postprandial TG when compared to plant-based SFA (palm olein) whereas Panth *et al*. (2019) found that plant-based SFA resulted in lower postprandial TG when compared to two sources of animal-based SFA (butter, lard).

These findings by Teng *et al*. (2011) and Panth *et al*. (2019) are contradictory and there were several key differences between the two study designs. First, Teng *et al*. (2011) recruited an exclusively male sample and employed a 3-day washout period between meal trials, while Panth *et al*. (2019) recruited equal amounts of males and females and employed a 1-week washout period between meal trials. Considering the brief washout period utilized by Teng *et al*. (2011), the effects of the dietary fat in the preceding meal trial may have carried over to the subsequent meal trial, thus influencing the postprandial response and interfering with the evaluation of a singular source of dietary fat. Additionally, Teng *et al*. (2011) utilized a meal higher in total kcal and percent of kcal from fat (~754 total kcal; 60% fat, 33% CHO, 7% protein) when compared to Panth *et al*. (2019) (~660 total kcal; 53% fat, 40% CHO, 5-7% protein). Teng *et al*. (2011) also instructed participants to abstain from consuming high-fat foods the day before the meal trials and administered a low-fat meal for the dinner preceding the day of the meal trial, while Panth *et al*. (2019) alternatively asked participants to consume the same meal the night before each meal trial. Lastly, the postprandial assessment period employed by Teng *et al*. (2011) consisted of baseline,

1, 2, 3, and 4 hours post-meal, whereas Panth *et al*. (2019) measured TG at baseline, 2, 3, 4, and 6 hours post-meal. Teng *et al*. (2011) may not have been able to capture the entire postprandial response, considering that postprandial TG tend to peak around 2-4 hours post-meal consumption and return to post-absorptive values around 6 hours post-meal (Bansal *et al*., 2007).

Factors Influencing the Postprandial Lipemic Response

Mixed meals contain varying amounts of macronutrients and micronutrients, which modulate physiological processes of digestion, absorption, and metabolism of fatty acids (Lorenzen *et al.*, 2007, Hazim *et al.*, 2014, Kay *et al.*, 2007). The use of laboratory-derived fat mixtures and lipid emulsions in the place of mixed meals is a common feature in studies assessing postprandial lipemia (e.g. Mekki *et al.*, 2002), particularly in those evaluating the effects of specific types of fatty acids or sources of dietary fat on postprandial lipemia. Several of the studies that have observed differences in postprandial lipemia based on source or type of dietary fat have utilized laboratory-derived fat mixtures or lipid emulsions (Calabrese *et al*., 1999; Dubois *et al.*, 1994; Dubois *et al.*, 1998). Considering that individuals do not consume these dietary fat sources in isolation or as a component of lipid emulsions in daily living, testing the effects of different fats within a mixed meal may be a more practical and appropriate approach. Our study, as well as others, tested the lipemic effects of different fat sources in the context of true-to-life mixed meal and did not observe differences across meal trials. If the various dietary fat sources used in this study were isolated in laboratory-derived fat mixtures, and thus the effects of macro- and micronutrients were removed, it is possible that differences in postprandial TG between various dietary fat sources may have been observed in the present study.

We observed a strong correlation between BMI and TG tAUC. Men had significantly higher BMI than women and no females were overweight or obese. This difference in BMI could explain sex-based differences across meal trials in postprandial lipemia. In agreement with our

findings, Kasai *et al.* (2003) found that men with a greater BMI (≥ 23 kg/m^2) compared to men with a lower BMI (<23 kg/m^2) exhibit greater postprandial lipemia in response to a HFM. In contrast, Hansson *et al.* (2019) did not find that BMI or sex significantly altered the postprandial TG response to various types of dairy fat rich in SFA. However, the study population (n = 31) consisted of 70% women and 30% men and therefore may not have been sufficient to establish a relationship between sex and postprandial TG in response to different fat sources. In addition, the median BMI was 23.6 kg/m^2 (range: 21.0-25.8). Consequently, the range of BMI may have been too narrow to establish a relationship between BMI and postprandial TG.

The majority of studies that found various sources of dietary fat influence postprandial lipemia differently included a sample of only male participants (Mekki *et al.*, 2002; Sun *et al.*, 2018; Calabrese *et al.*, 1999; Teng *et al.*, 2011). We also observed greater postprandial lipemic responses in men for all meal trials when compared to women. This finding adds to the notion that sex is an important modifying factor with regard to postprandial lipemia. There are well-known sex-based differences in visceral adipose tissue accumulation, with women generally storing less adipose tissue in the visceral region than men. Women tend to store fat in the gynoid regions (hips/breasts/thighs), while men tend to store fat primarily in the android regions (trunk/abdomen), and thus have a tendency to accumulate fat within visceral tissues. One study has suggested that this difference in visceral adipose accumulation between men and women is the primary explanation for the amplified postprandial response observed in men compared to women (Couillard *et al.*, 1999). Additionally, women with android obesity, both with normal and high fasting TG, exhibit a more pronounced and deleterious postprandial TG response when compared to women with gynoid obesity with normal fasting TG (Mekki *et al.*, 1999), further supporting the influence of sex on postprandial lipemia via body composition differences.

In addition, men tend to display a less favorable lipid profile, characterized by low HDL-C and high fasting TG concentrations when compared to women (Couillard *et al*., 1999). In the

present study, men had higher fasting LDL-C concentrations, but similar HDL-C compared to women. Although not statistically significant (but perhaps clinically significant), men generally reported with higher fasting TG concentrations (mean difference: 30.4 mg/dl) when compared to women. High fasting TG have been associated with a greater postprandial TG response, owing to a potentially delayed or decreased clearance of TG during the postprandial period (Couillard *et al.*, 1998). In this context, we found that men exhibited a greater postprandial TG peak compared to women. In addition to body composition, apparent differences in fasting metabolic concentrations may be a potential reason men displayed greater TG throughout the postprandial period compared to women in the present study.

Strengths

A strength of this study was the use of a "true-to-life" mixed HFM challenge, in contrast to many studies examining postprandial lipemia that use lipid emulsions or laboratory-derived lipid formulations. The meal used in the present study was also scaled to body weight and resembled a meal individuals might typically eat at a social gathering. This consideration is important because many postprandial studies utilize meals that are unrealistically high in calories, particularly calories from fat, and are not standardized to body weight. Therefore, this study allowed for the comparison of different dietary fats with regard to postprandial lipemia in a realistic context. This study also consisted of a balanced sample with regard to sex (5 M/ 5 F). Several studies similar in design had a predominately or exclusively male sample population. Another strength of this study was the robust postprandial assessment protocol, whereby we quantified the postprandial response serially every hour for 6-hours post-meal.

Limitations

A limitation of this study was only measuring blood lipids and glucose. Examining the size of circulating CM and concentrations of either intestinally derived apoB-48 and/or

endogenous apoB-100, in addition to blood lipids and glucose, may have been valuable with regard to answering our research question. Next, all of our participants were young and presented few CVD risk factors. Thus, features of atherosclerotic development, including exaggerated and prolonged postprandial lipemia, may not have been prominent enough to detect differences between meal trials, especially when considering the "true-to-life" meal used. Additionally, although this study found consistent sex-based differences in postprandial TG, it was not designed to address these differences. Lastly, the lack of body composition measurement beyond BMI was a limitation of the present study.

Conclusion and Future Directions

In our study, the effect of various sources of dietary fat, namely plant- and animal-based SFA, on postprandial lipemia did not differ. Sex-based differences regarding the postprandial lipemic response to the meal trials were observed and there was a strong correlation between BMI and TG tAUC, supporting the notion that sex and BMI are important factors that modulate the acute postprandial lipemic response. It is worth noting that our null findings on the effects of different fat sources within a mixed meal on postprandial lipemia were in a sample of young healthy individuals. Future studies should investigate the effects of these various dietary fat sources on postprandial lipemia in populations at risk for CVD or with existing CVD. In more at-risk individuals with a larger postprandial response, differences in TG between different sources of fat may be more apparent. Overall, the magnitude of postprandial lipemia in response to a realistic mixed meal is likely modulated by several interrelated dietary factors, such as the amount of fat, energy density, and the heterogeneous mixture of macro- and micronutrients, rather than the specific type or source of dietary fat alone. Future studies should continue to focus on delineating between various sources of animal-based SFA (dairy- vs. meat-based) with regard to CVD risk, both in an acute (postprandial) and chronic context

	Weight (g)	Energy (kcal)	Protein (g)	Fat (g)	CHO (g)
Sauce	257	577	5	52	25
Bread	28	78	3	1	16
Pasta	33	124	6	1	24
Total	318	780	14	54	65

Table 1. Test fats and meal composition. Data are representative of the test meal composition for a 60 kg participant.

	Total (n = 10)	Men (n = 5)	Women (n = 5)	p-value
Age (years)	23.8±7.2	24.4±1.5	23.2±0.8*	0.03
Weight (lbs)	168.7±55.6	208.5±50.9	128.8±19.4	0.01
Height (cm)	171.5±10.1	176.0±9.8	167.0±9.1	0.10
BMI (kg/m²)	23.8±1.3	30.3±7.4	20.7±1.7*	0.02
Fasting TG (mg/dL)	69.4±35.9	84.6±47.3	54.2±9.3	0.21
Fasting Glucose (mg/dL)	87.3±5.8	87.4±5.3	87.2±6.9	0.96
Fasting TOTAL-C (mg/dL)	184.0±35.2	195.2±42.2	172.8±26.3	0.44
Fasting LDL-C (mg/dL)	93.3±30.9	114.2±16.3	72.4±28.2*	0.02
Fasting HDL-C (mg/dL)	62.5±20.7	55.6±26.1	69.4±12.9	0.30
MVPA (minutes)	152.5±17.3	166.9±7.9	138±24.4	0.51
Steps/day	7934.6±747.7	7444.6±1024.3	8424.6±107.6	0.68

Table 2. Participant characteristics.
Metabolic outcomes represent fasting data averaged across the four meal trials. Data are presented as mean ± SD. *Indicates significant differences between men and women ($p < 0.05$). MVPA, moderate-vigoroous physical activity; TG, triglycerides; MLI, metabolic load index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; TOTAL-C, total cholesterol.

	Butter	*Coconut Oil*	*Olive Oil*	*Canola Oil*	*p-value*
Triglycerides					
Peak (mg/dL)	152.0±96.3	125.0±55.5	143.3±86.7	142.4±71.6	0.36
Time to peak (hours)	2.2±0.8	3.0±1.5	2.8±1.1	2.7±1.3	0.23
tAUC (mg/dL 6 hr)	671.7 ± 407.7	569.9 ± 250.3	651.2 ± 417.5	628.5 ± 284.1	0.33
iAUC (mg/dL 6 hr)	630.3 ± 85.2	616.5 ± 88.4	639.8 ± 94.3	629.4 ± 140.7	0.14
Glucose					
Peak (mg/dL)	96.5±16.7	95.0±12.6	97.5±12.5	98.4±14.9	0.76
Time to peak (hours)	3.2±1.8	2.4±1.9	2.5±1.8	2.5±2.3	0.48
tAUC (mg/dL 6 hr)	513.6±66.4	495.5±64.7	512.5±38.9	504.6±49.9	0.60
iAUC (mg/dL 6 hr)	5.1±27.0	-15.3±41.9	-19.8±19.8	19.1±46.2	0.26
Metabolic Load Index					
Peak (mg/dL)	241±105.4	208.8±60.5	230.4±99.2	231.3±231.3	0.24
Time to peak (hours)	2.7±1.1	2.7±1.4	2.9±1.2	3.2±1.9	0.64
tAUC (mg/dL 6 hr)	1185.2±447.7	1065.5±302.4	1163.7±448.9	1158.9±367.8	0.12
iAUC (mg/dL 6 hr)	260.7±239.9	163.1±151.6	219.1±222.1	181.9±228.6	0.08
TOTAL-C					
Peak (mg/dL)	176.9±27.1	168.7±47.9	195.1±37.2	194.1±38.6	0.12
Time to peak (hours)	3.2±2.3	3.6±2.4	4.3±1.8	2.2±2.3	0.09
tAUC (mg/dL 6 hr)	1012.2±163.2	954.9±283.9	1055.7±194.3	1109.8±230.6	0.11
iAUC (mg/dL 6 hr)	13.6±41.5	23.7±33.9	43.2±56.6	5.7±61.9	0.37
LDL-C					
Peak (mg/dL)	103.9±24.9	106.7±30.5	109.0±35.9	112.0±31.9	0.66
Time to peak (hours)	2.4±2.2	3.5±2.8	3.3±2.5	2.6±2.1	0.59
tAUC (mg/dL 6 hr)	550.5±131.4	552.2±176.9	557.5±177.7	597.6±187.8	0.62
iAUC (mg/dL 6 hr)	-9.6±108.4	36.8±105.4	42.1±179.7	59.9±197.2	0.72
HDL-C					
Peak (mg/dL)	58.8±14.9	63.8±20.4	62.1±17.8	65.7±22.3	0.19
Time to peak (hours)	3.4±2.7	3.7±2.0	3.5±2.4	2.2±2.4	0.52
tAUC (mg/dL 6 hr)	320.1±79.2	347.9±107.5	338.5±98.3	356.6±116.8	0.23
iAUC (mg/dL 6 hr)	3.3±18.4	18.2±36.3	4.9±22.4	-18.5±46.1	0.16

Table 3. Postprandial metabolic outcomes for the four meal trials.
Data are presented as mean ± SD. There were no differences between meals for all analyses ($p > 0.05$). TG, triglycerides; MLI, metabolic load index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; TOTAL-C, total cholesterol; tAUC, total area under curve; iAUC, incremental area under the curve.

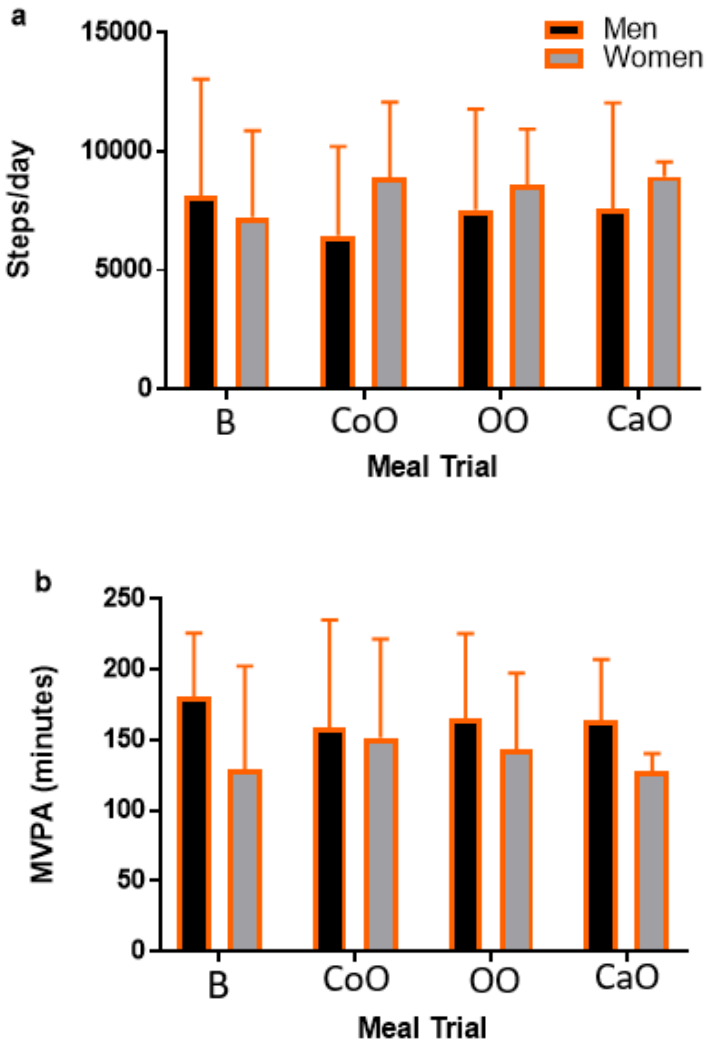

Figure 1. Pre-trial physical activity.
Physical activity in (a) steps/day and (b) MVPA for 48-72 hours before each meal trial, stratified by sex. Within each meal trial, there was no difference between men and women in physical activity in either MVPA or steps/day ($p > 0.05$). Similarly, within sex, there was no difference in physical activity across meal trials ($p > 0.05$). MVPA, moderate-vigoroous physical activity; B, butter; CoO, coconut oil; OO, olive oil; CaO, canola oil.

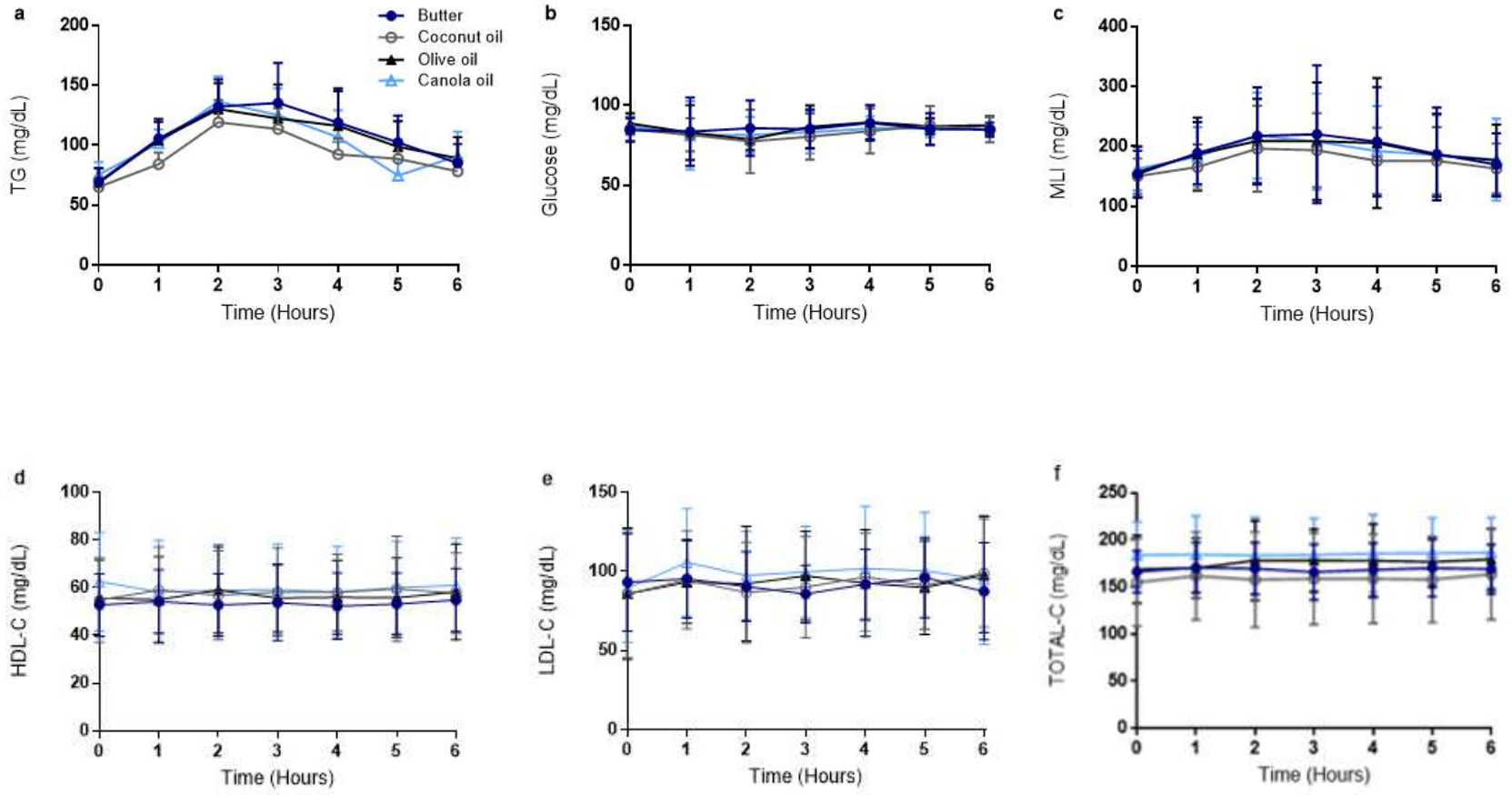

Figure 2. Postprandial metabolic responses.
Metabolic responses in the four meal trials at baseline and hourly throughout the postprandial period for (a) TG, (b) glucose, (c) MLI, (d) HDL-C, (e) LDL-C, and (f) TOTAL-C. Closed circles indicate B meal trial, open circles indicate CoO meal trial, closed triangles indicate OO meal trial, and open triangles indicate CaO meal trial. Error bars indicate SD. TG, triglycerides; MLI, metabolic load index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; TOTAL-C, total cholesterol; B, butter; CoO, coconut oil; OO, olive oil; CaO, canola oil.

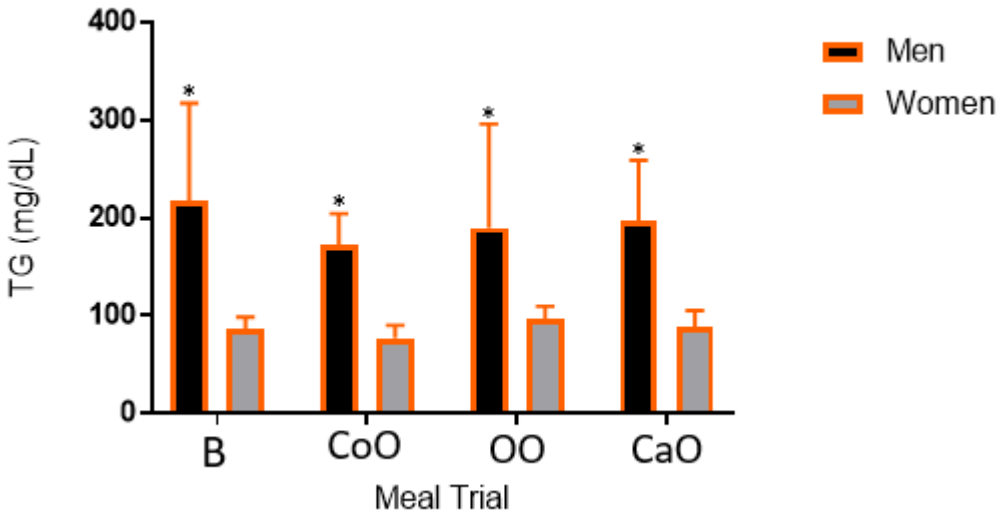

Figure 3. Peak triglyceride responses based on meal and sex.
Peak TG responses for meal trials when stratified by sex. *Indicate differences between men and women for a specific meal trial ($p < 0.05$). TG, triglycerides; B, butter; CoO, coconut oil; OO, olive oil; CaO, canola oil.

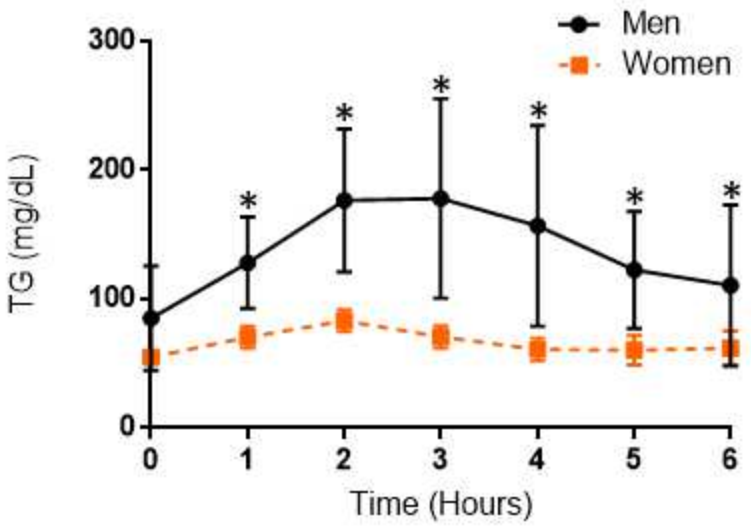

Figure 4. Consolidated postprandial triglyceride responses in men and women.
Average TG responses across meal trials at baseline and hourly throughout the postprandial period in men and women. *Indicate differences between men and women at a specific time point ($p < 0.05$) based on *post hoc* pairwise comparison. TG, triglycerides; B, butter; CoO, coconut oil; OO, olive oil; CaO, canola oil.

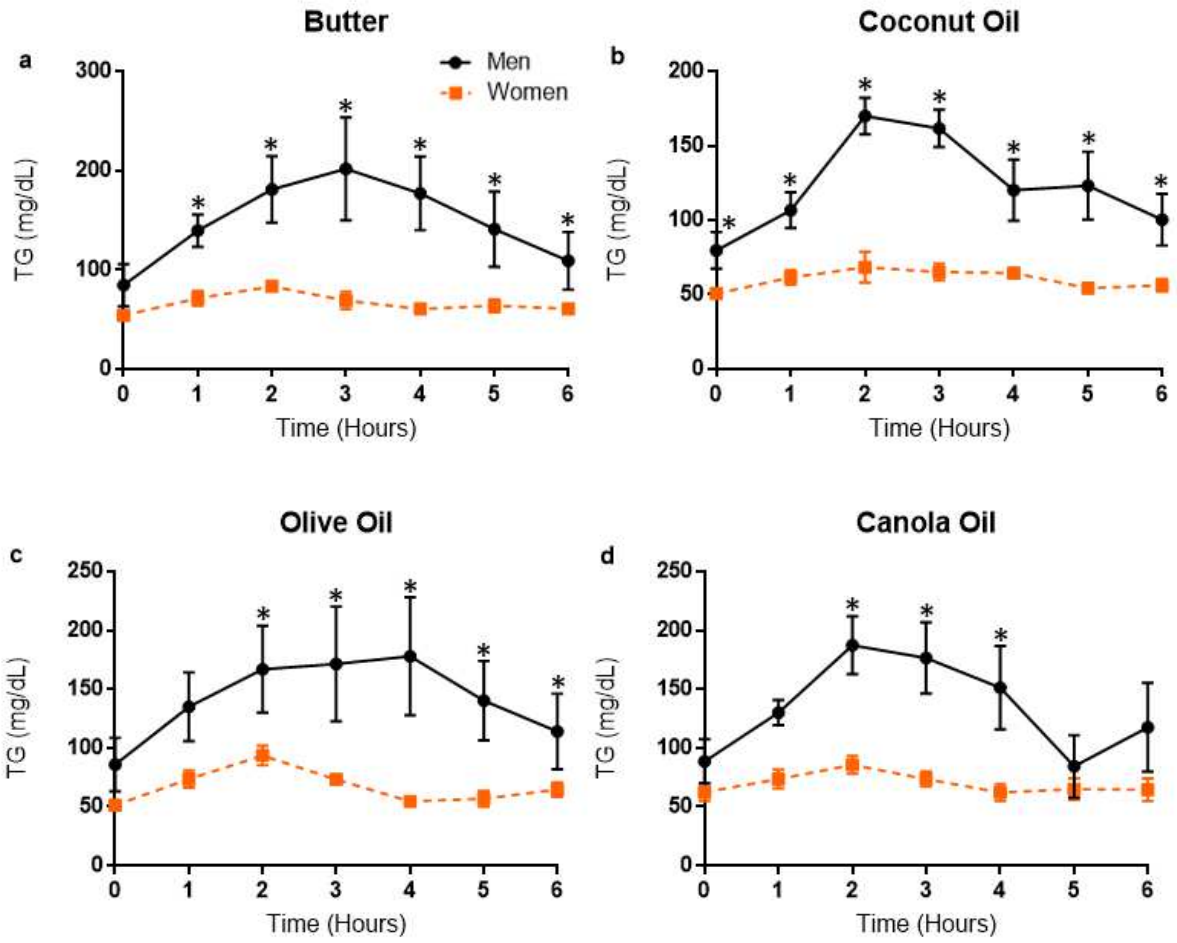

Figure 5. Postprandial triglyceride responses in men and women based on meal trial.
TG responses in men and women for each meal trial at baseline and hourly throughout the postprandial period. (a) TG response for B meal trial; (b) TG response for CoO meal trial; (c) TG response for OO meal trial; (d) TG response for CaO meal trial. *Indicate differences between men and women at a specific time point ($p < 0.05$) based on *post hoc* pairwise comparison. TG, triglycerides; MLI, metabolic load index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein; TOTAL-C, total cholesterol; B, butter; CoO, coconut oil; OO, olive oil; CaO, canola oil.

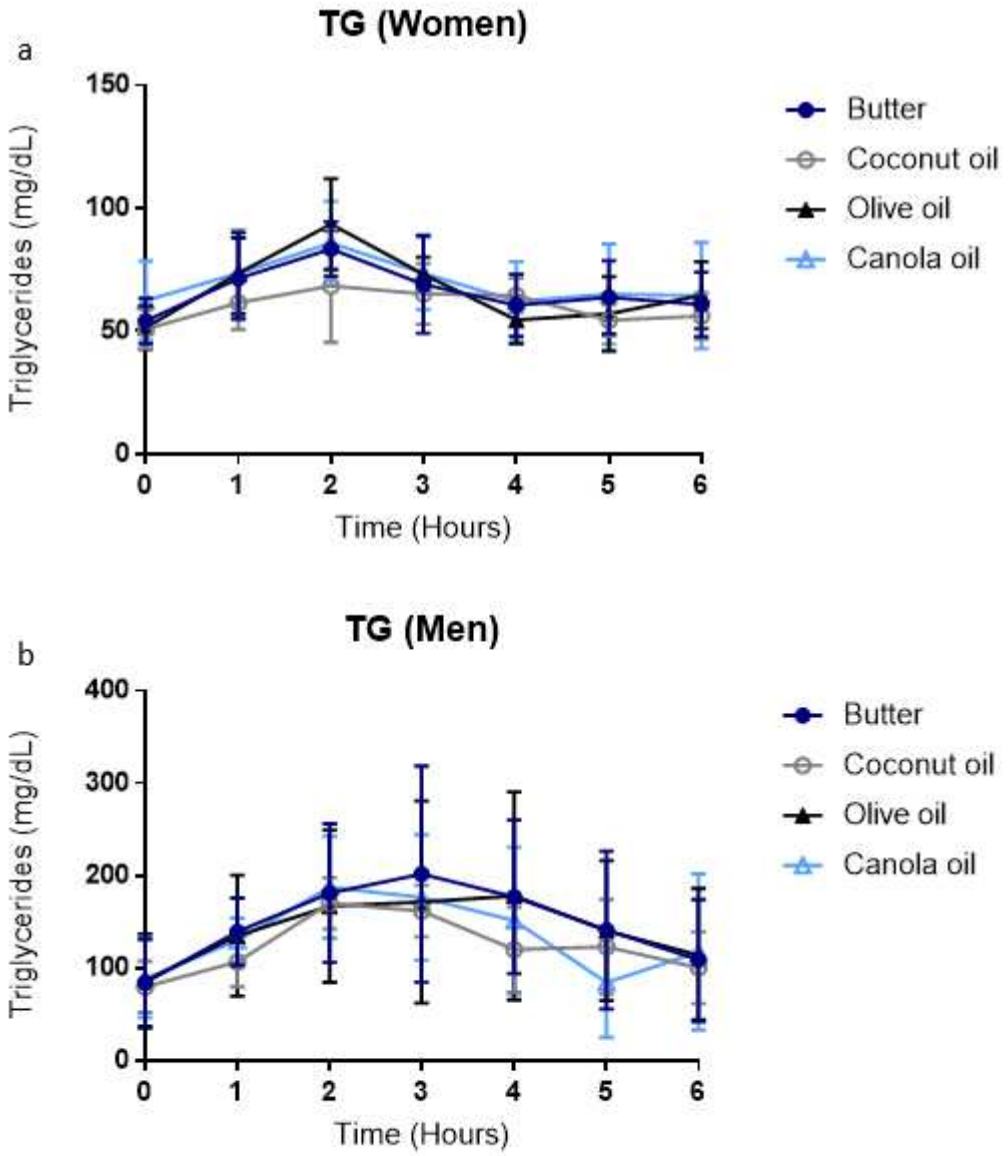

Figure 6. Postprandial triglyceride responses based on sex.
Metabolic responses in the four meal trials at baseline and hourly throughout the postprandial period stratified by sex for TG. Closed circles indicate B meal trial, open circles indicate CoO meal trial, closed triangles indicate OO meal trial, and open triangles indicate CaO meal trial. Error bars indicate SD. TG, triglycerides.

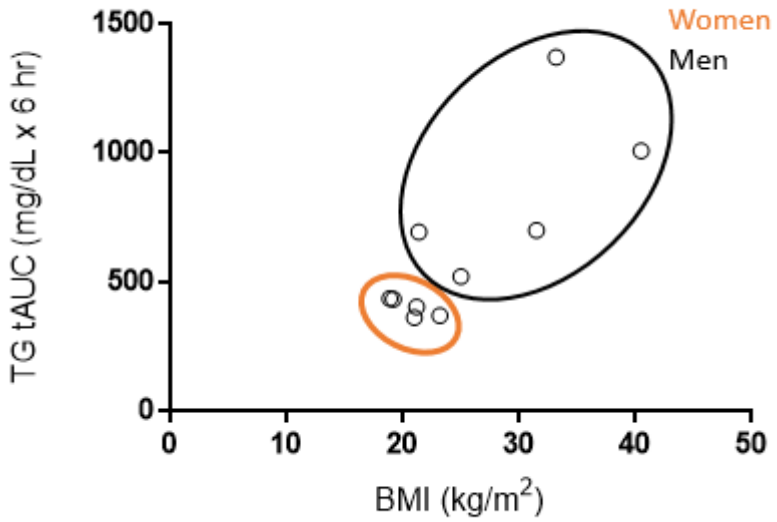

Figure 7. Correlation between TG tAUC and BMI.
Data are means of TG tAUC for each participant (averaged across the four meal trials) and BMI (kg/m^2) value for each individual participant. There was a significant positive correlation between BMI and TG tAUC ($r = 0.79$, $R^2 = 0.63$, $p = 0.006$). BMI, body mass index; TG tAUC, triglyceride total area under the curve.

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