DETERMINANTS OF POSTPRANDIAL TRIGLYCERIDES ACROSS THE SPECTRUM OF AGING

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Abstract: Although elevated postprandial triglycerides (TG) are a risk factor for heart disease, and older adults exhibit greater postprandial lipemia (PPL) than younger adults, it is unknown how postprandial lipid tolerance changes as people age. This cross-sectional study examined postprandial TG responses across the aging spectrum and how this was influenced by lifestyle and risk factors. We recruited individuals evenly distributed between the ages of 50-89, with a balance of males and females. Participants completed diet and physical activity questionnaires, body composition and flow-mediated dilation (FMD) assessments, and an abbreviated fat tolerance test (AFTT). Following a 10-hour overnight fast, a blood draw was performed before and four hours after consumption of a high-fat meal (9 kcal/kg) to determine fasting and postprandial TG. Fifty-six participants (Age Groups: 50s n = 15; 60s n = 15; 70s n = 15; 80s n = 11) completed the study. Fasting TG across age groups did not differ (p=0.63; 50s: 99.7 ± 50.1 mg/dL; 60s: 114.3 ± 71.1 mg/dL; 70s: 102.9 ± 45.0 mg/dL; 80s: 86.9 ± 39.5 mg/dL). There was also no difference (p=0.40) in 4-hour TG across age groups (50s: 162.9 ± 76.9 mg/dL; 60s: 181.9 ± 99.9 mg/dL; 70s: 130.8 ± 82.0 mg/dL; 80s: 130.8 ± 60.6 mg/dL). FMD results did not differ across groups (50s: 4.06 ± 1.88%; 60s: 4.21 ± 1.60%; 70s: 3.23 ± 1.68%; 80s: 3.53 ± 1.23%). Moderate-to-vigorous physical activity minutes (MVPA) differed (p=0.01) across groups (50s: 190.5 ± 46.07; 60s: 177.6 ± 63.87; 70s: 135.8 ± 41.88; 80s: 139 ± 54.35). Variables significantly correlated with 4-hour TG included BMI, visceral adiposity, ALT, glucose, and alcohol. In Backward Elimination regression, the most predictive variables of 4-hour TG across age groups were postprandial glucose (p=0.01), ALT (p=0.007), and alcohol intake (p=0.04). Across four major decades (50s-80s), age and physical activity were not found to determine PPL. However, we identified ALT, postprandial glucose, and alcohol intake as key determinants of 4-hour TG. Future studies should aim to further understand the relationship between liver health, insulin resistance, alcohol intake, and PPL across the aging spectrum.

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CHAPTER I

INTRODUCTION

In 2000, older adults represented just under 11% of the total U.S. population (Yazdanyar and Newman, 2010). As advancements in health and understanding of human pathophysiology improve, that number is expected to increase. By the year 2050, older adults between the ages of 65 and 84 are expected to represent 16% of the population (Yazdanyar and Newman, 2010). Moreover, individuals over age 85 will increase from 6 million to 19 million (Yazdanyar and Newman, 2010).

This increase in proportion of older adults will undoubtedly give rise to a greater burden of cardiovascular disease (CVD) in the United States. It has been well-established that the greatest incidence of CVD occurs in older adults. According to the American Heart Association (AHA, 2013), 66% of total heart disease deaths occur in people over the age of 75 years. The economic burden of CVD is also of concern. AHA estimated that the US spent over $318 billion on healthcare costs related to CVD in 2016. This cost is expected to more than double by 2035. These issues highlight the need for an increased understanding of the unique challenges associated with older adulthood and how to mitigate heart disease risk within the aging population.

Aging encompasses both social and physiological changes that can make it difficult to maintain a healthy lifestyle. Major influential factors include health status, functional status, cognition, and environment (Bernstein and Munoz, 2012). These factors can impact overall feasibility to engage in physical activity and eat a nutritionally adequate diet, two generally accepted behaviors that modify chronic disease risk. The most common risk factors for CVD include high blood pressure, elevated blood cholesterol, physical inactivity, excess alcohol intake and tobacco use (CDC, 2019). While these variables can exist at any age from adolescence to adulthood, older adults appear to be particularly vulnerable to mortality from CVD-related events.

Consequently, it is important to establish effective screening tools to determine who is most at risk for heart disease. Common indices of heart disease used to assess risk in clinical settings include elevated total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG), as well as decreased high-density lipoprotein (HDL) cholesterol. These markers are typically measured in the fasted state to avoid the influence of food consumption on well-established recommendations for these variables. However, even if these fasting values appear normal, postprandial TGs (serum TG concentrations after consumption of a meal) are more strongly associated with declining cardiometabolic function and all-cause mortality than fasting TGs alone (Kolovou et al., 2011; Katsanos, 2014). This abnormally elevated TG response is termed postprandial lipemia (PPL). Moreover, older adults tend to exhibit greater PPL when compared to younger adults (Katsanos, 2014), which could indicate greater predisposition to CVD.

Despite this observation, it is not entirely clear why older adults experience greater PPL than younger adults, or if this response differs across the spectrum of aging.

Diet pattern and physical activity, commonly cited culprits of behavior-related risks for CVD, can influence the postprandial response (Emerson et al., 2018; Rivellese, Bozzetto, and Annuzzi, 2009). Within the older adult population, metabolic changes that occur could contribute to increased PPL as well (Katsanos, 2014), likely augmented by lifestyle changes and alterations in functional status. There are many variables that have the ability to influence the postprandial TG response, but it is still not entirely clear what are the most predictive determinants of PPL in the aging population. Therefore, the purpose of this study is to evaluate the postprandial TG response within the older adult population and to identify which factors best predict PPL. Our hypothesis is that postprandial TGs will increase as age increases, and optimal lifestyle factors and body composition will be associated with more favorable outcomes.

CHAPTER II

LITERATURE REVIEW

Overview of Cardiovascular Disease

Prevalence and Statistics

Cardiovascular disease (CVD) remains the leading cause of death worldwide, responsible for more than 850,000 deaths in the United States in 2017 (AHA, 2020). According to the CDC, 12.1% of the U.S. population has been diagnosed with heart disease, which equates to over 30 million people (2017). Furthermore, it is estimated that 1 in every 4 deaths in the U.S. are attributable to CVD (CDC, 2019). Consequently, heart disease remains a significant problem in the U.S. and around the globe, despite increasing knowledge about its pathophysiology and risk factors.

Pathophysiology

CVD is an umbrella term for diseases that affect blood vessels of the cardiovascular system, such as coronary artery disease, atherosclerosis, stroke, and peripheral artery disease (NIH, 2019). A chronic state of hypercholesterolemia and inflammation influences the development and progression of CVD (Hansson, 2005). Atherosclerosis, or a prolonged buildup of plaque within the intima region of a blood

vessel, is a hallmark of CVD. This process begins with an excess of LDL cholesterol, which deposits cholesterol into vascular walls (Hansson, 2005).

Once retained in the arterial wall, LDL are susceptible to oxidation, leading to an inflammatory response. Oxidized LDL are taken up by macrophages, a type of immune cell, which release pro-inflammatory cytokines (Li and Mehta, 2005). These lipid-laden macrophages are termed "foam cells," a characteristic feature of atherosclerotic lesions. These cells intensify immune responses through the communication between type 1 helper cells (Th1 cells) and expression of adhesion molecules on endothelial cells (Hansson, 2001). This infiltration of immune cells leads to the progression of inflammation and tissue damage, and ultimately, atherosclerotic plaque buildup.

As CVD progresses, this accumulation of plaque may become increasingly vulnerable to rupture and blockage. There are many mechanisms that contribute to this tendency, many of which stem from changes in macrophages. Once macrophages become foam cells, these pro-inflammatory cells will produce enzymes and growth factors which promote the progression and stabilization of plaque (Badimon and Vilahur, 2014). Simultaneously, as the fatty lesion grows, hypoxia-inducible factor (HIF-1α) will code for vascular endothelial growth factor (VEGF) to stimulate the growth of new blood vessels which will also support the continued growth and stability of the plaque (Badimon and Vilahur, 2014). Additionally, vascular smooth muscle cells (VSMCs) will promote the formation of collagen and a fibrous cap; however, as CVD progress, VSMCs will reduce in number and matrix metalloproteases (MMPs) released from foam cells and apoptosis of VSMCs will promote the degradation of fibrous caps (Davies, 1996). If a plaque ruptures and a thrombus forms, blood platelets will rush to the area in an attempt

to sequester the damaged tissue, which will promote blood clotting and subsequent reduction or complete loss of blood flow to the affected area, a common manifestation of cardiac events (Badimon and Vilahur, 2014).

Risk Factors

Although not exclusively, CVD risk is heavily influenced by several modifiable lifestyle behaviors. AHA classifies risk factors into three different categories: major, modifiable, and contributing (2016). Major risk factors, or risk factors that are non-modifiable, include age, sex, ethnicity, and genetics. All of these variables can modify an individual's risk of developing CVD regardless of lifestyle or chronic behaviors. For example, the majority of myocardial infarctions occur in individuals above 65 years of age; additionally, Americans of Mexican and African descent are known to have a higher risk of CVD regardless of lifestyle behavior (AHA, 2016). Risk factors that can be modified, or controlled, include cigarette smoking, high cholesterol, hypertriglyceridemia, high blood pressure, physical inactivity, and presence of obesity (CDC, 2019). Furthermore, other lifestyle factors that may contribute to these modifiable risk factors include stress, alcohol consumption, and chronic diet (CDC, 2019).

It has been well-established that prolonged dietary exposure can either contribute to or prevent the development of CVD and atherosclerosis, with particular emphasis on fruit and vegetable intake. Some components that are known to have a protective effect include fiber, antioxidants, and phytosterols, all of which are present in high amounts in fruits and vegetables. Fiber intake has been shown to have a protective effect against CVD due to its ability to bind bile acids during digestion, leading to a reduction in circulating cholesterol in the body, a result of the requirement of cholesterol in bile acid

synthesis in the liver (Torres, et al., 2015). Consumption of 2-10 grams of soluble fiber per day has been shown to lower LDL cholesterol by 7% (Brown, Rosner, Willet, and Sacks, 1999). Phytosterols have a comparable mechanism of action, due to their similar molecular composition to cholesterol. Phytosterols are known to compete with cholesterol for absorption, leading to decreased absorption of dietary cholesterol (Patch, Tapsell, Williams, and Gordon, 2006).

Another dietary component that can have a notable effect on LDL cholesterol are omega-3 fatty acids, a type of polyunsaturated fatty acid (PUFA). These omega-3 fatty acids have anti-inflammatory effects in the body, decelerating the effects of atherosclerosis. Omega-3 fatty acids can reduce LDL retention in the intima, and decrease the recruitment of inflammatory cytokines and monocyte adherence in the arterial endothelium (Chang and Deckelbaum, 2013). Antioxidants can also have a protective effect through their action on free radicals. Free radicals are unstable molecules characterized by an unpaired election. These molecules can directly cause inflammation and expression of pro-inflammatory cytokines through oxidative stress. Dietary antioxidants stabilize these reactive oxygen species (ROS) by donating electrons (Kaliora, Dedoussis, and Schmidt, 2006). Additionally, folic acid reduces CVD risk through its action on homocysteine. Homocysteine is an intermediate compound in the metabolism of B vitamins folate and B_{12}. If folate intake is low, homocysteine can accumulate in the blood and increase risk for CVD. Some effects of elevated homocysteine in the body include increased platelet aggregation, inactivation of anticoagulants, and increased production of superoxide free radical (Brown and Hu, 2001).

Additionally, high doses of antioxidant vitamin C are also associated with decreased CVD risk by stimulation of collagen production, which may decrease risk of thrombus rupture (Torres et al., 2015). Another example is lycopene, a carotenoid commonly found in tomatoes. Evidence suggests that lycopene can prevent the oxidation of LDL and reduce intima thickness, a proxy measurement for vascular plaque accumulation (Palozza, Parrone, Simone, and Catalano, 2010). Alternatively, dietary components that promote CVD include saturated fats, added sugar, and refined grains – all of which are commonly associated with the typical "western diet." Conversely, the Mediterranean diet, which is characterized by high intake of fruit, vegetables, fish, whole grains, unsaturated fatty acids, and low intake of red meat, saturated fat, and added sugar has gained popularity to aid in the prevention of CVD (Widmer, Flammer, Lerman, and Lerman, 2015).

In addition to diet, physical activity can also have a preventative effect on CVD. AHA recommends 150 minutes of moderate-to-vigorous-intensity aerobic activity per week (2018). Exercise acts beneficially on plasma lipids, insulin sensitivity, and blood pressure to reduce risk of CVD. Research indicates that exercise not only raises HDL and lowers plasma TG, LDL, and very-low-density lipoprotein (VLDL) concentrations, but can also lead to an increase in LDL size, which reduces their ability to penetrate the endothelium and become oxidized (Kraus et al., 2002). Exercise improves insulin sensitivity, as well as lowers serum insulin (Nystoriak and Bhatnagar, 2018). Also, although the exact mechanism is unclear, studies have demonstrated an increased translocation of GLUT4 (the primary glucose transporter in myocytes) to the cell

membrane independent of insulin following exercise (Goodyear et al., 1990). Additionally, blood pressure, although acutely increased during the period of exercise itself, decreases in response to chronic exercise training, leading to reduced CVD risk (Fagard, 2001). Thus, although exercise itself acts as a stressor on the body, it prompts the cardiovascular system to increase its ability to transport oxygen to muscles. This will result in adaptations of the cardiovascular system, such as improved vasodilation and increased ventricle wall thickness (Breisch, et al., 1986). These adaptations, if implemented long-term, can be an effective measure for the prevention of CVD.

Metabolic Syndrome and Dyslipidemia

Metabolic syndrome represents a cluster of preventable symptoms that significantly increase overall risk for CVD, likely resulting at least in part from chronic lifestyle factors. Key components of metabolic syndrome include obesity, glucose intolerance, hypertension, and dyslipidemia (Eckel, Grundy, and Zimmet, 2005). The International Diabetes Federation (IDF) provides a universally accepted cluster of systems that warrant a diagnosis of metabolic syndrome. Metabolic syndrome can be diagnosed if an individual expresses central obesity (waist circumference of >40 inches in men, and >35 inches in women) and two of the following factors: raised TGs (≥150 mg/dL), reduced HDL cholesterol (<40 mg/dL in males; <50 mg/dL in females), high blood pressure (systolic BP ≥130 mmHg; diastolic BP ≥85 mmHg), insulin resistance, and raised fasting plasma glucose (≥100 mg/dL). Although the exact prevalence remains unknown, the CDC estimates that 30% of the US population meet the criteria for a diagnosis of metabolic syndrome (2017). Central obesity, or visceral adiposity, is important when evaluating the presence of metabolic syndrome, as the location of fat is metabolically

significant due to the portal hypothesis. It is theorized that visceral fat can increase free fatty acids and pro-inflammatory adipokines directly to the liver via its close proximity, and then systemically to the rest of the body (Shah, et al., 2014). Moreover, visceral fat can be more predictive of metabolic syndrome than weight or BMI alone (Shah, et al., 2014). Thus, visceral fat is especially adverse with regard to CVD risk promotion.

Although all features of metabolic syndrome are highly interrelated, the underlying mechanism of metabolic syndrome likely stems from insulin resistance (Eckel, Grundy, and Zimmet, 2005). One consequence of obesity is increased circulation of fatty acids and TGs, which can build up in glucose-sensitive tissues; consequently, this can interfere with intra-cellular insulin signaling (Rask-Madsen and Kahn, 2012). Furthermore, in the fed state, the body no longer needs to rely on stored energy in adipose tissue; therefore, another function of insulin apart from cellular glucose uptake is suppression of lipolysis. If insulin signaling is impaired, so is suppression of lipolysis – therefore circulating fatty acids in the bloodstream are further elevated (Eckel, Grundy, and Zimmet, 2005). This relationship between fatty acids and impaired insulin signaling can ultimately lead to dyslipidemia, glucose intolerance, and even hypertension, all of which are manifestations of metabolic syndrome.

Dyslipidemia, defined as abnormal cholesterol and lipoprotein concentrations in circulation, can have systemic effects on the body, particularly within the context of metabolic syndrome. Because insulin resistance can increase fatty acid circulation, this can lead to an increase in fatty acid translocation to the liver, and subsequent increase in VLDL secretion (Grundy, 1998). Insulin resistance can also result in the reduction of lipoprotein lipase (LPL) enzyme activity, which will decrease the clearance of VLDL,

further promoting elevated VLDL in circulation. This altered LPL activity can also cause elevated TGs, which in the form of VLDL, can activate cholesterol ester transfer protein (CETP) and reduce HDL concentrations (Grundy, 1998). Furthermore, individuals with dyslipidemia who have TG concentrations of >2.0 mmol/L (>177 mg/dL) will often have a predominance of small, dense LDL, which is even more atherogenic than normal LDL (Grundy, 1998). Smaller, more dense LDL particles will be more able penetrate the subendothelial space and be subject to oxidation, which will activate the atherosclerotic process. Hence, a lifelong state of disease-promoting behaviors ultimately increases the body's susceptibility to CVD through these related mechanisms, which can be difficult to reverse.

Vascular Function and FMD

Given the prevalence of CVD, efforts have been made to determine risk in a non-invasive manner. One approach is a process called flow-mediated dilation (FMD), which was originally developed in 1992 (Celermajer et al., 1992). FMD is an assessment of endothelial function of the cardiovascular system, commonly performed by viewing the brachial artery via doppler ultrasound. Evidence shows that endothelial dysfunction precedes atherosclerotic plaque development, which makes FMD an advantageous tool to assess CVD development early in the disease process (Thijssen, et al., 2019). Measurement of FMD involves placement of a blood pressure cuff around the forearm, and inducing ischemia via vascular occlusion (Harris, et al., 2010). Following an appropriate amount of time (usually 4-5 minutes), the blood pressure cuff is released and vasodilation in response to hyperemia occurs. FMD is expressed as the percent change in diameter of the blood vessel following the occlusion period or ischemia, which provides

an indication of overall vascular function (Harris, et al., 2010). A greater dilatory response is considered reflective of better vascular function. The arterial endothelium contains biologically active molecules which influence its overall function, characterized by a balance of vasodilatory and vasoconstrictive compounds (Seals et al., 2014). Healthy endothelial function is largely dependent on nitric oxide (NO) production, a key compound for induction of vasodilation (Seals et al., 2014). Vasodilation is an important biological function, as it widens the blood vessels in response to a stimulus, such as exercise, lowering blood pressure and systemic vascular resistance, thereby increasing blood flow when necessary. An increase in blood flow or shear stress will trigger the expression of phosphokinase A, an enzyme which activates endothelial nitric oxide synthase (eNOS) (Sessa, 2004). This process will generate NO from L-arginine, which will migrate to the tunica media, or middle layer of the blood vessel, and activate the enzyme guanylate cyclase (Harris, et al., 2010). Guanylate cyclase will convert guanosine triphosphate to guanosine monophosphate, which will induce vasodilation of blood vessels, and reduce blood pressure (Harris, et al., 2010). This change in dilation is expressed as a percent change in diameter from baseline following prolonged occlusion of the brachial artery. Endothelial dysfunction is associated with impaired NO bioavailability and an increased expression of adhesion molecules on the endothelium, such as vascular cell adhesion molecule 1 (VCAM-1), and consequently, a reduced ability to vasodilate. As a result, endothelial dysfunction will result in a lower FMD percentage. Thijssen, et al., (2019) suggest that a 1% increase in FMD equates to an 8-13% reduction in CVD risk.

It is important to consider how CVD risk factors such as diet and physical activity affect endothelial function and FMD. Regular exercise has been shown to improve endothelial function through increased expression of NO and a decreased expression of ROS (Francescomarino et al., 2009). Furthermore, NO production has been suggested as the trigger for the release of endothelial progenitor cells (EPCs) from bone marrow, which can improve endothelial function by promoting the growth of new blood vessels and vascular repair (Francescomarino et al., 2009).

Similar to exercise, notable dietary components that can influence endothelial function include omega-3 fatty acids, antioxidants, and folic acid. Omega-3 fatty acids present in fish, walnuts, and flaxseed have been shown to decrease VCAM-1 and increase NO production (Brown and Hu, 2001). Antioxidant vitamins, such as C and E, can reduce monocyte adhesion molecules, promote vasodilation, and reduce oxidative stress (Brown and Hu, 2001). Elevated homocysteine levels, caused by insufficient folic acid, can down-regulate NO, inactivate anti-coagulants, and increase production of the superoxide free radical, all of which will ultimately impair vasodilatory effects of the endothelium (Brown and Hu, 2001). As a result, prevention of endothelial dysfunction through behavioral measures can delay the onset of CVD and early mortality.

Additionally, a decline in endothelial function has been connected with serum TG concentrations in adults (Kajikawa et al., 2016). A large cross-sectional study found that even when adjusting for confounding variables, endothelial function, which was measured by FMD, was negatively associated with TG concentrations at 1.20 mmol/L (106 mg/dL) when compared with 0.71 mmol/L (63 mg/dL) (Kajikawa et al., 2016). It is

hypothesized that these TG rich lipoproteins (TRLs) in serum are able to penetrate the arterial wall and cause an inflammatory response, resulting in monocyte recruitment and foam cell formation (Kajikawa et al., 2016). This study serves to further strengthen the relationship between endothelial dysfunction, TG concentrations, and overall CVD risk, with FMD being a valuable tool to assess the clinical significance of this relationship.

Overview of Lipid Metabolism

Following lipid digestion and absorption, free fatty acids, glycerol, cholesterol, and various fat-soluble vitamins are packaged into chylomicrons, which can then be absorbed via the lymphatic system (Davidson, 2019). A chylomicron is a lipoprotein, a hydrophobic molecule with the main function of transporting lipids to different tissues in the body (Stipanuk and Caudill, 2012). Other types of lipoproteins include VLDL, LDL, and HDL. Furthermore, apolipoproteins are proteins present on lipoproteins and are responsible for stabilization and receptor communication of the lipoprotein (Stipanuk and Caudill, 2012).

Once absorbed, chylomicrons travel through the lymphatic system and into the circulatory system. Rich in TG, chylomicrons carry the apolipropteins ApoB-48, ApoC-II, and ApoE, and deliver TG to adipose and muscle tissues, where they are hydrolyzed via the action of the endothelium-bound enzyme LPL (Stipanuk and Caudill, 2012). ApoC-II present on the chylomicron mediates the activation of LPL and subsequent uptake of free fatty acids by tissues (Stipanuk and Caudill, 2012). Through this process, chylomicrons are then converted into chylomicron remnants, now with relatively lesser TG and greater cholesterol content, and are transported to the liver facilitated by ApoE (Davidson, 2019). Excess lipids and cholesterol from chylomicron remnants as well as

endogenous lipids in the liver are then synthesized into VLDL, with ApoB-100 being the major apolipoprotein present (Stipanuk and Caudill, 2012). VLDL, similar to chylomicrons, will transport TG to peripheral tissues where they are hydrolyzed by LPL. Through this process, VLDL will become intermediate-density lipoprotein (IDL) and then LDL, which carries a predominance of cholesterol (Stipanuk and Caudill, 2012).

The main function of LDL, known colloquially as "bad" cholesterol, is to transport cholesterol to peripheral tissues. LDL receptors present on endothelial cells communicate with ApoB-100 and LDL particles are endocytosed into extra-hepatic tissues (Stipanuk and Caudill, 2012). This process is susceptible to becoming atherogenic when LDL is in excess (Davidson, 2019). On the other hand, while LDL promotes cholesterol esterification and storage within cells, HDL is primarily involved in a process often termed "reverse cholesterol transport." HDL is synthesized in the liver and is able to remove excess cholesterol from peripheral cells, which is why it is characterized as being anti-atherogenic (Davidson, 2019). CETP mediates the uptake of cholesterol by HDL. Once inside the cell, lecithin cholesterol acyltransferase (LCAT) is responsible for esterifying free cholesterol that is taken up by HDL (Stipanuk and Caudill, 2012).

Postprandial Triglyceride Response

Elevated TG are exceedingly common among the U.S. population, with an estimated 31% having serum concentrations >150 mg/dL, which is defined as being borderline high (Miller et al., 2011). Ethnicities that report the highest rates of hypertriglyceridemia are Mexican Americans and non-Hispanic whites (Miller et al., 2011). Obesity, sedentary behavior, type 2 diabetes, and metabolic syndrome are all

highly correlated with elevated TG concentrations (Miller et al., 2011). In 2001, the National Cholesterol Education Program (NCEP) updated fasting triglyceride classifications as follows: <150 mg/dL, desirable; 150-199 mg/dL, borderline-high; 200-499, high, and >500, very high.

Postprandial lipemia (PPL) refers to an abnormally high concentration of triglycerides in the blood following consumption of a high-fat meal. TGs can be measured in both fasting and non-fasting (or postprandial) states. Research has shown that peak postprandial TG concentrations are more strongly correlated with cardiovascular events and mortality than fasting TG concentrations (Bansal et al., 2007). Therefore, it is useful to measure TG status in the non-fasting state, as this is the state that individuals are in for the majority of the day (Katsanos, 2014). Some known modifiers of PPL include diet, physical activity level, and smoking (Rivellese, Bozzetto, and Annuzzi, 2009). There is currently not a well-defined cut-off point for non-fasting TGs. However, it is apparent that non-fasting or postprandial TG, which can be measured up to 8 hours after a meal, are more strongly correlated with CVD risk over fasting TGs (Kolovou, et al, 2011)**.**

Although some research suggests that TG concentrations <175 mg/dL in the non-fasting state is more optimal for health and prevention of cardiovascular outcomes (White, et al., 2015), a postprandial response of <220 mg/dL after administration of a high-fat meal is considered desirable (Kolovou et al., 2011)**.** Clinical measurement of PPL is characterized by administration of a high-fat meal, and measuring an individual's lipid profile both before and after the meal to determine their metabolic response. This is often termed a fat tolerance test (FTT). While there is not an official, standardized FTT,

common features include having the participant fast 8-10 hours prior to the baseline blood draw, consuming a sizeable portion of fat (70-80 grams), and obtaining repeated blood samples several hours after the meal (Kolovou, et al, 2011). According to the Copenhagen General Population Study, peak TG levels occur at approximately 4 hours in the postprandial state (Nordestgaard et al., 2007; Weiss et al., 2008). Findings from our laboratory agree with this observation regarding the timing of peak TG (Sciarrillo et al., 2018).

Postprandial lipemia can vary based on sex, body composition, and a variety of different lifestyle factors. For example, men typically have both a greater postprandial TG response and lower HDL concentrations than women, even when adjusted for weight (Couillard et al., 1999). It is thought that this difference may be due to visceral adiposity and a larger waist circumference in men than in women, supporting the idea that high visceral adiposity leads to adverse metabolic outcomes (Couillard et al., 1999). Moreover, a study by Matikainen et al. (2007) found postprandial lipid concentrations to be positively associated with liver fat content, and negatively associated with adiponectin levels, an anti-inflammatory adipokine. There may also be a genetic component to the postprandial TG response. Studies have investigated the influence of genes that code for LPL, CETP, ABCA1, and IL-6, and how single nucleotide polymorphisms (SNPs) might lead to alterations in the postprandial TG response (Perez-Martinez et al., 2010). Individuals with certain allele variations in genes that code for apolipoproteins and enzymes involved in lipid metabolism can show an elevation or reduction in postprandial TGs; however, more research is needed as studies have varying results (Perez-Martinez et al., 2010). Regardless, there is a clear relationship between lifestyle behaviors and PPL,

including diet and physical activity. Many studies have assessed the impact of diet on PPL and CVD risk. For example, single-meal experiments have shown that addition of approximately 12 grams of fiber can substantially reduce postprandial TG response, whereas high-fat meals acutely increase postprandial TGs and affect endothelial function (Rivellese, Bozzetto, and Annuzzi, 2009). Previous studies have also compared high-carbohydrate diets with high fat (MUFA) diets. Results indicate that a high-carbohydrate meal, especially with the addition of fiber, results in reduced chylomicron formation and therefore reduced postprandial TG concentrations (Bozzetto et al., 2014). There is conflicting evidence regarding type of fat influencing TG response. While some evidence suggests EPA and DHA fatty acids reduce both fasting and postprandial TG levels, other studies are inconclusive to its effect (Damsgaard et al., 2008; Kelley et al., 2007). For example, when comparing different kinds of dietary fat (butter, coconut oil, olive oil, and canola oil), a study from our laboratory showed that postprandial TG responses did not differ significantly between meal trials (Sciarrillo et al., 2019).

Physical activity is also an important modifier of the postprandial response. It has been well-documented that acute exercise can reduce the postprandial TG response. For example, a randomized, controlled trial saw an 8% reduction in postprandial lipid concentrations following a high-fat meal with 30 minutes of aerobic exercise when compared with no exercise (Ho, Dhaliwal, Hills, and Pall, 2011). Perhaps more compelling, in individuals with TG concentrations exceeding >150 mg/dL, long-term implementation of moderate-intensity activities can attenuate TG concentrations by up to 15-20% in the fasted state (Miller et al, 2011). However, a study by Kim et al. (2016) found that consecutive days of prolonged sitting can negate the lipid lowering effects of

exercise, even in individuals who are regularly physically active. This finding is significant, considering the high prevalence of sedentary behavior among adults. Consequently, maintaining physical activity behaviors throughout adulthood is crucial to sustain its protective effects.

Overview of Aging

The relationship between CVD and age cannot be ignored, as an estimated 83% of individuals over 80 years old have some form of CVD (Katsanos, 2014). Lifestyle changes across the spectrum of aging, including physical activity and diet, affect metabolic outcomes and subsequently, chronic disease in older adults. Currently, 1 in 4 adults over 50 are considered inactive, and at least 30% have at least 1 or more chronic disease (CDC, 2014). Presence of chronic disease can affect ability to engage in health promoting physical activity behaviors. Furthermore, older adults are at an increased risk for nutritional issues. Age-related declines in muscle mass and basal metabolic rate contribute to decreased energy needs and caloric intake. Socioeconomic status and ability to live independently can affect access to healthy foods and dietary quality. According to a study by the Academy of Nutrition and Dietetics, older adults do not meet the recommended requirements of many micronutrients including calcium, iron, B vitamins, and zinc, but exceed the recommendations for fat, sodium, and added sugars (Bernstein and Munoz, 2012). Fruit and vegetable consumption, which strongly correlates with higher diet quality and a lowered risk of chronic disease, can be hindered by functional limitations, presence of dysphagia, and financial hardships associated with retirement (Bernstein and Munoz, 2012). Therefore, due to these changes during aging (both

metabolic and behavioral), the importance of monitoring CVD risk during old age is critical.

Postprandial Lipemia in Older Adults

There is significant evidence to support the idea that metabolic changes during older adulthood contribute to greater PPL, and a number of theories attempt to explain the mechanism behind this (Katsanos, 2014). One possible explanation is the role of LPL, the endothelial enzyme responsible for TG clearance in muscle and adipose tissue. Reduced LPL activity is associated with raised TG concentrations, both fasting and postprandial, and lower HDL-C concentrations (Bey, Areiquat, Sano, and Hamilton, 2001). LPL activity can decrease with age, likely augmented by a loss of muscle mass, which could account for decreased TG clearance in older adults, although the extent to the effect of this change is disputed (Katsanos, 2014). It is important to note that sedentary behavior can also correlate with a reduction in LPL activity, independent of age (Zderic and Hamilton, 2006)**.** In this context, it has been well-documented that older adults regularly engage in more sedentary behavior than younger counterparts (Clark and Sugiyama, 2015)**.** Older adults might be limited in their ability to engage in adequate exercise due to decreases in muscle mass and presence of chronic conditions, which could contribute to a decrease in LPL activity. In fact, up to a 60% reduction in LPL concentrations have been reported in the elderly when compared with young adults, particularly in skeletal muscle (Bey, Areiquat, Sano, and Hamilton, 2001). Given that skeletal muscle can account for up to ~45% of total body mass, this could significantly influence the metabolic response to TGs in the body (Bey, Areiquat, Sano, and Hamilton, 2001).

Age-associated changes in the liver can also contribute to increased PPL in older adults. For example, increased fat content of the liver associated with aging might contribute to increased production of endogenous VLDL synthesis (Couteur et al., 2007). Furthermore, older adults may have increased levels of ApoB-100, which would accelerate VLDL secretion by the liver, contributing to increased plasma FFAs and PPL (Millar et al., 1995). Also, increased visceral adiposity surrounding the liver may also contribute to increased FFA flux via the portal vein hypothesis (Nelson et al., 2007). These mechanistic changes are important to consider when determining why older adults might be of an increased risk for PPL. Furthermore, Katsanos (2014) suggests that PPL is a better predictor of CVD and all-cause mortality rather than total cholesterol or HDL concentrations alone, prompting the need to further understand the relationship between PPL and aging.

Physical activity can also be an important modifier of the TG response following consumption of a high-fat meal in older adults. Emerson et. al. (2018) showed that when comparing TG response between younger active, older active, and older inactive adults, differences were seen in all 3 groups. While the younger, active adults showed the lowest TG response over both of the older groups, suggesting that age can influence PPL regardless of activity, the older active adults still showed a favorable TG response over the older inactive adults, suggesting that physical activity can modify this response independent of age (Emerson et al., 2018). It is important to note that in this study, every group (regardless of age and activity level) had optimal fasting TG levels (<150 mg/dL),

which highlights the importance of measuring postprandial TG responses as opposed to only fasting concentrations.

Vascular Dysfunction in Older Adults

Vascular function is known to progressively decline with age due to a variety of mechanisms and independent of other risk factors. During aging, NO bioavailability decreases, and cyclooxygenase (COX) derived vasoconstrictors increase (Brandes et al., 2005). This imbalance of vasoactive factors leads to increased production of ROS, specifically superoxide anion, which is theorized to be one driving force of endothelial dysfunction in older age (Brandes et al., 2005). Insufficient production of antioxidant enzymes amplifies this response (Seals et al., 2014). Likewise, L-arginine is an important precursor to NO. Some animal studies have shown that an increase in arginase activity, an enzyme that breaks down L-arginine, also contributes to decreased NO production (Berkowitz et al., 2003). Although the exact mechanism is less clear, decreased availability of L-arginine precursor might also contribute to an increase in vascular dysfunction in the aging population. Furthermore, aging triggers upregulation of pro-inflammatory pathways. Aging increases expression of the pro-inflammatory cytokine TNF-α, which promotes mitochondrial dysfunction, increased NADPH oxidase, and a decrease in eNOS (Bruunsgaard et al., 2000). This will lead to increased ROS, decreased NO, activation of NF-$\kappa\beta$, and other proinflammatory mediators that promote vascular damage and apoptosis (Herrera et al., 2010).

During aging, these cellular alterations can lead to endothelial cell senescence, or the state in which these cells can no longer divide properly as a result of telomere alteration (Brandes et al., 2005). This phenomenon can be accelerated by age-related

endothelial dysfunction and increased apoptosis (Brandes et al., 2005). Some evidence suggests that NO bioavailability is connected to the function of telomerase reverse transcriptase (TERT), an enzyme important for proper function of telomeres. Decreased activity of the TERT enzyme has been linked to decreased NO production during aging, and increased cellular senescence; likewise, increasing NO activity can delay this response (Vasa et al., 2000). As a result, endothelial function tends to decline with age independently of other risk factors, which leads to increased prevalence of CVD and other chronic diseases in old age; however, behavior modification appears to delay or alter this response (Seals et al., 2014). For example, aerobic exercise has been shown to preserve endothelial function in men primarily through mechanisms associated with increased NO bioavailability, reduction of oxidative stress, and suppression of NF-κB signaling (Seals et al., 2014). Diets characterized by low levels of sodium, saturated fat, cholesterol, and high amounts of fruits, vegetables, potassium, magnesium, and calcium improved endothelium-dependent dilation (EDD) by activating pathways that promote homeostasis and down-regulation of oxidative stress and inflammation (Seals et al., 2014).

With respect to FMD, a study with almost 2,800 subjects with a median age of 78 found that the average FMD percentage was 3.0% in women and 2.4% in men (Yeboah et al., 2007). For reference, an FMD response of between 5-15% is indicative of healthy arterial dilation (Faulx, Wright, and Hoit, 2003). This study found that declining FMD response had similar predictability to future CVD-related events as other traditional risk factor assessment methods (Yeboah eta l., 2007). Furthermore, a different study showed that while older adults tend to show less favorable FMD than younger adults, presumably

due to age-related declines in endothelial function, older adults who maintain optimal fitness levels exhibit similar FMD to young individuals (Black et al, 2009). This indicates that vascular function can be preserved with optimal lifestyle behaviors, even in older age. Since FMD can assess presence of endothelial dysfunction, a key step in the beginning of atherosclerosis, and is a quick, non-invasive tool, it possesses clear utility as an assessment tool for CVD risk in older adults.

Remaining Questions

While there is an established connection between aging and CVD risk, and past studies have showed a clear distinction between younger adults and older adults with regard to a number of CVD risk factors, there is less of a focus on the entire spectrum of aging. Specifically, it has been well-established that older adults exhibit greater postprandial lipemia compared to younger counterparts (Emerson et al., 2018). However, it is unknown how PPL differs across the spectrum aging. Further, given the numerous changes that occur during the aging process, including body composition, insulin sensitivity, activity level, diet, and liver health, it is unclear which age-related changes are most influential of PPL. In the absence of such knowledge, targeted approaches for mitigating excessive PPL in older adults will remain elusive.

Purpose and Hypotheses

Therefore, this study aimed to determine the postprandial triglyceride response to an abbreviated fat tolerance test (AFTT) across four major decades of aging, and to identify factors that best predict these fasting and postprandial metabolic outcomes. To achieve this purpose, we tested older adults in strata based on age: 50s, 60s, 70s, and 80s. This approach allowed us to compare PPL and potential determinants across the spectrum

of aging. We hypothesized that the postprandial TG response would be greater across increasing age categories. Furthermore, across age groups, we hypothesized that more optimal postprandial TG would be associated with greater diet quality, increased physical activity, and more optimal body composition.

CHAPTER III

METHODOLOGY

Participants

A total of 56 participants were recruited for the study. Recruitment methods included word of mouth, email, and in-person announcements in assisted living facilities. Forty-five participants were equally distributed across three of the four decades of aging we assessed, specifically 50s (n = 15), 60s (n = 15), and 70s (n = 15). Within each of these groups, there was an approximately equal distribution between males and females as well (each group: n = 7-8 males and 7-8 females). Due to Covid-19 restrictions during the later stages of data collection, recruitment was unable to be completed within the 80s age group, and as a result, this group included a total of 11 participants. We were not able to obtain postprandial values for one female in the 80s group due to phlebotomy difficulties, so postprandial metabolic results are only representative of 10 participants in that group. There was still an equal sex distribution with 6 males and 5 females. Participants were excluded from the study if they were not ambulatory, used tobacco products, or if they had any electrical implants, such as a pacemaker. However, participants were not excluded based on medication usage or presence of chronic disease.

Overall Study Design

This study featured a cross-sectional design using a human research model, which assessed variables at a single point in time. Participants were assessed through a total of

two laboratory visits. In the first visit (initial assessment), following informed consent of all study protocol and obligations, participants were primarily assessed for body composition using bioelectrical impedance analysis and were given an accelerometer as well as a variety of questionnaires to assess diet and physical activity behaviors. The second visit consisted of a metabolic assessment, which included FMD and an AFTT.

Initial Assessment

The first visit to the laboratory included measurement of body composition and assessment of diet and physical activity behaviors. Following arrival to the laboratory and explanation of informed consent, participants were measured for height (Seca 213 portable stadiometer), waist circumference (Seca tape measure), and blood pressure (Omron automated blood pressure cuff). Blood pressure was taken whilst sitting at least twice to ensure an accurate measurement and was measured a third time if the first two readings had a high degree of variability (>5 mmHg). Then, the participant was assessed using bioelectrical impedance analysis (BIA; Seca mBCA 514). Bioelectrical impedance works by sending small, insensible electrical currents throughout the body as the participant is standing, which assesses resistance between different types of tissues, such as body fat and muscle. Participants were instructed to remove any metal on the body before the assessment such as jewelry, belts, or loose change to ensure accuracy of the device. The Seca mBCA 514 measured body mass, calculates body mass index (BMI), and estimates body fat percentage, fat-free body mass, skeletal muscle mass, and visceral adiposity via BIA.

Prior to leaving the laboratory, participants were given five validated questionnaires to complete outside of the laboratory: a standard, 130-item food frequency

questionnaire (FFQ), which assessed chronic diet over the past 12 months, the international physical activity questionnaire (IPAQ), which assessed physical activity over the previous 7 days, a past year physical activity questionnaire (PYPAQ), which assessed physical activity over the previous 12 months, and a lifetime physical activity questionnaire (LPAQ), which assessed both current and chronic physical activity behaviors. Finally, an ActiGraph accelerometer was placed on the participant's non-dominant wrist for 5 days, and they were instructed to leave it on at all times. Accelerometry is utilized to directly assess current physical activity in steps per day and moderate- to vigorous-intensity physical activity minutes per day.

Metabolic Assessment

The second visit to the laboratory, the metabolic assessment, was scheduled during the first visit, at least five days after the first to ensure adequate time to wear the accelerometer. Most second visits occurred approximately one week after the first. Additionally, participants were instructed to avoid planned exercise at least 24 hours prior to the second visit and arrive in the laboratory following a 10-hour overnight fast. The second visit consisted of measurement of FMD and an AFTT, as described in detail below.

FMD Protocol

Immediately following arrival to the laboratory, participants lied on a medical bed for 5-10 minutes in dim lighting to acclimate to the room and ensure accurate resting heart rate and blood pressure. To begin FMD, the right arm was positioned perpendicular to the body and a pediatric blood pressure cuff was attached approximately two inches from the wrist. Using Doppler ultrasound (Mindray Z5; Mindray Medical International;

Shenzhen, China), a linear probe was used to visualize the brachial artery in the upper arm, and once a good image was established, the image was recorded. Baseline measurements were recorded for the first two minutes without inflation of the blood pressure cuff. After two minutes had passed, the blood pressure cuff was inflated to 220 mmHg in order to occlude blood flow for the following four minutes. Then the blood pressure cuff was released, and the dilation of the brachial artery and subsequent recovery was measured for 4 minutes, totaling a 10-minute video. Protocols used have been previously validated by Harris et al., 2010. The video was then analyzed using commercial software (Cardiovascular Suite; Quipu; Pisa, Italy).

AFTT Protocol

While the participant was still lying in a supine position, a fasting blood draw was taken in the forearm using a 21-gauge venipuncture needle. Blood was drawn into a 5 mL lithium heparin vacutainer. The whole blood sample was analyzed using a Piccolo Xpress clinical chemistry analyzer, using Lipid Panel Plus and Comprehensive Metabolic Panel discs. Lipid Panel Plus discs included the following analytes: alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol (CHOL), non-HDL cholesterol (nHDLc), glucose (GLU), HDL, LDL, VLDL, and TGs. Metabolic Panel discs included the following analytes: albumin (ALB), alkaline phosphatase (ALP), ALT, AST, blood urea nitrogen (BUN), calcium (Ca), chloride (Cl^-), creatinine (CRE), GLU, potassium (K^+), sodium (Na^+), bilirubin (TBIL), total carbon dioxide (tCO_2), and total protein/albumin-globulin ratio (TP). After the fasting blood draw was collected, the participant consumed a standardized high fat shake within 20 minutes. The participant was then allowed to vacate the laboratory for 4 hours, with instructions not to eat or drink

anything of caloric value or engage in any planned exercise during this time. However, participants were otherwise free to perform other activities of daily living. Upon returning, a follow-up 4-hour blood draw was taken to assess the participants' postprandial TG response. This AFTT protocol has been previously utilized and validated by our laboratory group (Sciarrillo et al., 2018).

The dairy-free, hypoallergenic high-fat shake, as the test meal for the AFTT, consisted of coconut cream, Hershey's chocolate syrup, and vegan protein powder. It was prepared the day before the participant arrived using body composition data from the initial assessment. To ensure consistency, it was prepared by the same person each time using the same equipment. The protein powder and chocolate syrup were measured by weight, and the coconut cream was measured in milliliters. The shake, which was calculated for each participant according to body weight (9 kcal/kg), consisted of 73% fat, 26% carbohydrate, and 1% protein, and was consumed in approximately 20 minutes. After preparation, the shake was refrigerated overnight prior to the metabolic assessment.

Statistical Analyses

Normality of data was assessed via Shapiro-Wilk formal normality test. A one-way analysis of variance (ANOVA), which compares multiple groups, was used to test for differences between age groups with regard to metabolic outcomes, body composition measurements, diet, physical activity, and FMD. For non-normal data, the non-parametric Kruskal-Wallis test was used. When appropriate, Tukey's post hoc test was used to compare individual means and adjust for multiple comparisons in order to reduce occurrence of type 1 error. Pearson correlation was used to test for association between potential explanatory variables (such as body composition, diet, and metabolic variables)

and 4-hour triglycerides. Regression analyses were used to determine the model and variables most predictive of 4-hour TG. All statistical tests were performed using GraphPad Prism 9 and IBM SPSS Statistics. Statistical significance was predetermined at $\alpha = 0.05$ for all analyses, except if Tukey's was run.

CHAPTER IV

RESULTS

Participant Characteristics

Participant characteristics are shown in **Table 1**. There were no significant differences in body composition variables across groups, including body mass, BMI, body fat %, fat-free mass %, or visceral adiposity (ps > 0.05). While systolic blood pressure was not significantly different ($p = 0.07$), diastolic blood pressure was statistically different across age groups ($p = 0.01$). Specifically, diastolic blood pressure in the 50s age group was significantly higher than the 60s, with a mean difference of 12.8 mmHg ($p = 0.04$), 70s, with a mean difference of 12 mmHg ($p = 0.03$), and the 80s age group, with a mean difference of 13.5 mmHg ($p=0.02$). While kidney markers blood urea nitrogen (BUN) and creatinine did not differ across age, liver enzyme alanine aminotransferase (ALT) was significantly different between groups ($p = 0.002$). The 50s age group had significantly elevated ALT over both the 70s and 80s group ($p = 0.03$, with a mean difference of 8.5 mg/dL and $p = 0.001$, with a mean difference of 9.4 mg/dL, respectively). The 60s age group also had elevated ALT compared to the 80s group ($p = 0.04$, with a mean difference of 6.6 mg/dL). While these significant differences exist, most participants fell within the reference range of 10-47 U/L. No differences were observed with regard to the liver enzyme AST ($p = 0.44$).

Table 1. Participant Characteristics by Age Group.

	50s	60	70s	80s	p-value
Sample size (Total N = 56)	15	15	15	11	N/A
Sex (M/F)	7M/8F	7M/8F	7M/8F	6M/4F	N/A
Age (years)	55.3 ± 2.5[a]	64.3 ± 3.3[b]	74.5 ± 3.1[c]	82.4 ± 1.6[d]	<0.0001
Height (cm)	170.3 ± 11.3	167.9 ± 12.6	169.1 ± 10.6	164.2 ± 9.8	0.57
Body mass (kg)	85.5 ± 17.1	80.7 ± 18.5	82 ± 18.6	67.7 ± 12.7	0.07
Body mass index (kg/m^2)	29.3 ± 4.7	28.4 ± 4.9	28.3 ± 5.5	24.8 ± 2.4	0.10
Body fat (%)	35.6 ± 7.6	36.9 ± 7.80	39.1 ± 8.3	36.6 ± 11.6	0.73
Fat Free Mass (%)	64.4 ± 7.5	63.1 ± 7.8	60.1 ± 8.3	63.1 ± 11.4	0.73
Systolic BP (mmHg)	133.3 ± 23.8	120.2 ± 13.8	136 ± 18.1	135.6 ± 13.1	0.07
Diastolic BP (mmHg)	91.4 ± 19.1[a]	79.5 ± 6.7[b]	79.3 ± 8.5[b]	77.9 ± 5.7[bc]	0.01
VAT (L)	2.6 ± 1.3	2.8 ± 1.6	3.3 ± 2	2.7 ± 0.9	0.92
Creatinine (mg/dL)	1.03 ± 0.21	0.97 ± 0.21	1.03 ± 0.44	0.95 ± 0.26	0.86
BUN (mg/dL)	14.67 ± 5.02	14.07 ± 3.35	16.53 ± 6.81	17.55 ± 3.56	0.17
ALT (U/L)	31.3 ± 11.1[a]	28.5 ± 12.2[ab]	22.9 ± 4.6[bc]	21.91 ± 3.05[c]	0.002
AST (U/L)	33.1 ± 6.8	31.6 ± 7.4	29 ± 4.9	30.6 ± 4.2	0.44

Statistical results for each variable represent findings of a one-way ANOVA (normal data) or Kruskal-Wallis test (non-normal data). Data are represented as Mean ± SD. Superscript letters demonstrate results of post hoc comparisons. Within a row, cells with similar superscript letters do not differ.
BP, blood pressure; BUN, blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Diet and Physical Activity

Diet data obtained via food frequency questionnaire are displayed in **Table 2.** There were no significant differences in fruit and vegetable (FV) intake, sugar sweetened beverage intake (SSB), meat intake, whole grain intake, alcohol intake, dairy intake, or dessert intake across age groups ($p > 0.05$). While total fruit and vegetable intake was not

significantly different, non-starchy vegetable intake differed across age strata (p = 0.02). Specifically, intake of non-starchy vegetables was significantly less in the 50s age group than in the 60s (p = 0.01). There were no other significant differences between groups, indicating that there was little diet variation across our study population.

Table 2. Diet Data Across Age Groups.

	50s	60s	70s	80s	p-value
FVs (frequency/day)	4.4 ± 1.7	7.7 ± 4.8	6.5 ± 3.6	6.0 ± 2.4	0.053
NS Vegetables (frequency/day)	2.7 ± 1.2[a]	4.8 ± 2.5[b]	3.6 ± 2[ab]	3.39 ± 1.6[ab]	0.02
SSBs (frequency/day)	0.3 ± 0.4	0.4 ± 0.5	0.9 ± 1.2	0.7 ± 0.8	0.28
Meat (frequency/day)	1.5 ± 0.6	2.1 ± 1.1	2.1 ± 2.3	1.3 ± 0.9	0.28
Whole Grain Intake (% grains)	20.7 ± 15.7	30.1 ± 16	33 ± 21.4	31 ± 14.1	0.23
Alcohol (frequency/day)	0.5 ± 0.7	0.5 ± 0.9	0.4 ± 0.5	0.4 ± 0.8	0.73
Dairy (frequency/day)	1.3 ± 1.1	1.8 ± 1.3	2.1 ± 1.4	2.2 ± 1.4	0.23
Dessert & Sweets (frequency/day)	1.0 ± 0.8	0.7 ± 0.4	0.8 ± 0.5	1.0 ± 0.8	0.66

Statistical results for each variable represent findings of a one-way ANOVA or Kruskal-Wallis test. Data are represented as Mean ± SD. Superscript letters demonstrate results of post hoc comparisons. Within a row, cells with similar superscript letters do not differ. FV, fruit and vegetable; NS, non-starchy; SSB, sugar-sweetened beverages.

Physical activity data obtained by both questionnaires and accelerometers is shown in **Table 3.** While self-reported current and lifetime physical activity did not differ across groups, past year physical activity data (PYPAQ) expressed at MET hours did differ significantly across groups (p = 0.03). Post hoc comparisons indicated that the 70s and 80s groups differed (p = 0.01), with the 80s group being more physically active than the 70s group, with a mean difference of 2,789 MET-hours. Finally, accelerometry data revealed that minutes of moderate- to vigorous-intensity physical activity (MVPA) significantly different across age groups (p = 0.01). While there was a general decline in MVPA minutes

across age strata, post hoc analyses indicated that only the 50s age group differed significantly from the 70s age group (p = 0.03), with a mean difference of 55 minutes/day.

Table 3. Physical Activity Data Across Groups.

	50s	60s	70s	80s	p-value
Past Week MET-minutes	4877 ± 4073	3871 ± 3256	3818 ± 3978	6197 ± 4967	0.42
Past Year MET-hours	6893 ± 2579[ab]	6637 ± 4652[ab]	4851 ± 2889[a]	7640 ± 2786[b]	0.03
Lifetime MET-hours	129082 ± 81066	235935 ± 186799	195185 ± 149389	241693 ± 137348	0.16
Accelerometry, Steps/day	11359 ± 2328	10974 ± 3363	9413 ± 2624	10103 ± 3113	0.26
Accelerometry, MVPA/day	190.5 ± 46.07[a]	177.6 ± 63.87[ab]	135.8 ± 41.88[b]	139 ± 54.35[ab]	0.01

Statistical results for each variable represent findings of a one-way ANOVA or Kruskal-Wallis test. Data are represented as Mean ± SD. Superscript letters demonstrate results of post hoc comparisons. Within a row, cells with similar superscript letters do not differ. MET, metabolic equivalent; MVPA, moderate-vigorous physical activity minutes.

Metabolic Markers and Flow-Mediated Dilation

Fasting metabolic markers across age groups are shown in **Figure 1.** Two participants (13%) in the 50s age group had fasting TGs >150 mg/dL, and mean TG concentrations in this group were 99.7 ± 50.1 mg/dL. Seven participants in this group (47%) reported usage of statin medication, while eight did not. There were also two participants (13%) in the 60s age group with fasting TGs >150 mg/dL. Average TG concentrations were 114.3 ± 71.1 mg/dL in this group, with only 5 out of 15 participants (33%) reporting statin use. In the 70s group, two participants (13%) had fasting TG levels >150 mg/dL, and average TG concentration were 102.9 ± 45.0 mg/dL. Nine participants in this age strata (60%) reported statin usage, while six did not. Finally, only one participant in the 80s age group (9%) had fasting TGs of >150 mg/dL, with four (36%) reporting statin usage. The average TG concentrations in this group were 86.9 ± 39.5 mg/dL. There were

no significant differences in fasting TG concentration across groups ($p = 0.63$), and significance did not change after adjustment for statin usage.

Total cholesterol was not significantly different across age groups ($p = 0.16$), nor was fasting LDL-cholesterol ($p = 0.14$), HDL-cholesterol ($p = 0.26$), or VLDL-cholesterol ($p = 0.61$). Across all groups, 11 participants had total cholesterol >200 mg/dL; 21 had LDL >100 mg/dL; and 13 had HDL <50 mg/dL. Fasting glucose was also not significantly different across age groups ($p = 0.06$). Average blood glucose was 98.8 ± 7.0 mg/dL in the 50s age group, 105.0 ± 9.7 mg/dL in the 60s age group, 104.2 ± 9.5 in the 70s age group, and 97.2 ± 6.8 in the 80s age group. Two participants in the 60s group reported having type 2 diabetes, and 1 in the 70s groups reported having pre-diabetes. Only one participant in the 60s age group with diabetes reported taking the glucose lowering medication metformin.

Postprandial values for TGs and glucose are also shown in **Figure 1.** Average 4-hour TG concentrations were 162.8 ± 76.9 mg/dL in the 50s age group, 181.9 ± 99.9 mg/dL in the 60s age group, 177.3 ± 82.0 mg/dL in the 70s age group, and 130.8 ± 60.6 mg/dL in the 80s age group. There were no significant differences in 4-hour TG concentrations across age groups ($p = 0.40$). The average change in TG concentration from baseline to 4 hours was 63.1 ± 36.8 mg/dL in the 50s group, 67.6 ± 46.4 mg/dL in the 60s group, 74.5 ± 45.4 mg/dL in the 70s group, and 43.5 ± 21.4 mg/dL in the 80s group. No significant differences in the change in TG concentrations from baseline were observed across age groups ($p = 0.30$). Postprandial glucose concentrations were significantly different across groups ($p = 0.04$). Average glucose concentrations after 4 hours were 95.0 ± 7.0 mg/dL in the 50s age group, 101.0 ± 7.8 mg/dL in the 60s age group, 100.3 ± 9.0 mg/dL in the 70s

age group, and 94.1 ± 5.0 mg/dL in the 80s age group. However, there were no significant post hoc comparisons for glucose concentrations in the postprandial state.

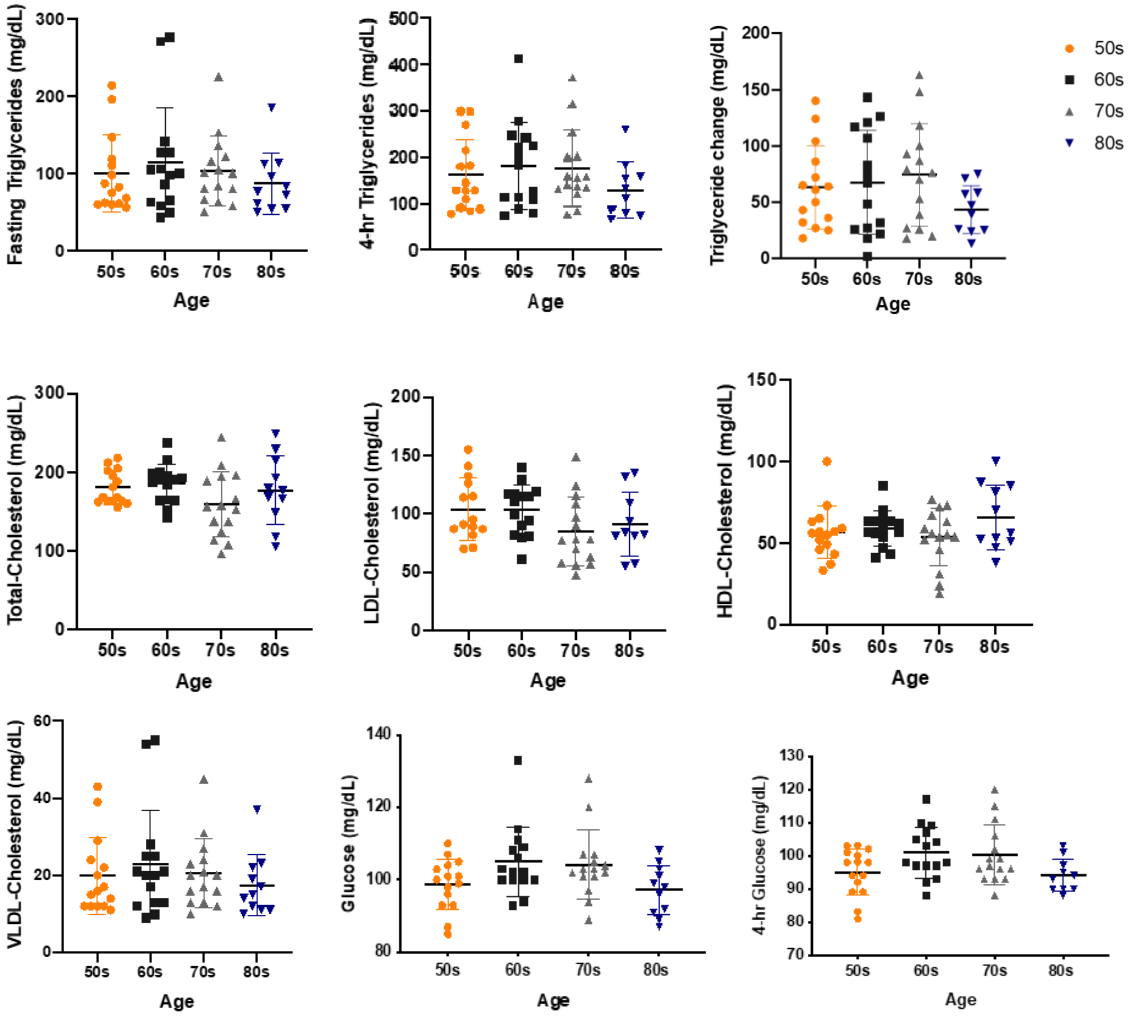

Figure 1. Metabolic Results Across Age Groups. Data are represented as individual data points as well as Mean ± SD.

FMD results across age groups are shown in **Figure 2.** Average FMD was 4.06 ± 1.88 % in the 50s age group, 4.21 ± 1.60 % in the 60s age group, 3.23 ± 1.68 % in the 70s age group, and 3.53 ± 1.23 % in the 80s age group. FMD values were not significantly different across age groups ($p = 0.34$). However, there was a weak, positive correlation between FMD percentage and steps/day (measured via accelerometer) across age groups

(p = 0.04; r = 0.27). There were no other significant correlations between FMD and physical activity outcomes (p > 0.05).

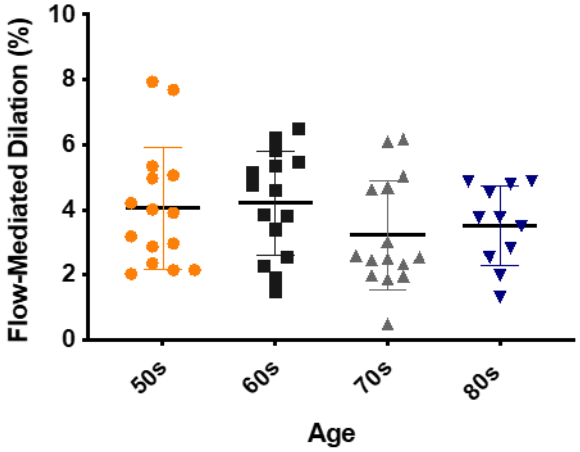

Figure 2. Flow-mediated dilation (FMD) results across age groups. Data are represented as individual data points as well as Mean ± SD. There were no significant differences (p > 0.05).

Significant Correlations across All Age Groups

Variables significantly correlated with postprandial TGs across all ages are shown in **Figure 3.** Multiple variables were significantly associated with 4-hour TGs. Body composition variables BMI (p = 0.02; r = 0.29) and visceral adipose tissue (p = 0.02; r = 0.31) were positively correlated with postprandial TGs. Metabolic markers positively associated with 4-hour TGs included VLDL (p = 0.0001; r = 0.89), fasting glucose (p = 0.04; r = 0.27), and 4-hour glucose (p = 0.009; r = 0.34). Fasting HDL was inversely associated with 4-hr triglycerides (p = 0.03; r = -0.29). Liver enzyme ALT was positively correlated with postprandial TGs (p = 0.005; r = 0.37), as was alcohol intake (p = 0.01; r = 0.33). Total fruit and vegetable intake were also positively correlated with 4-hour TGs (p = 0.04; r = 0.27). However, body fat percentage, blood pressure, blood urea nitrogen,

creatinine, LDL-cholesterol, FMD, and other dietary variables were not significantly correlated with 4-hour TGs ($p > 0.05$).

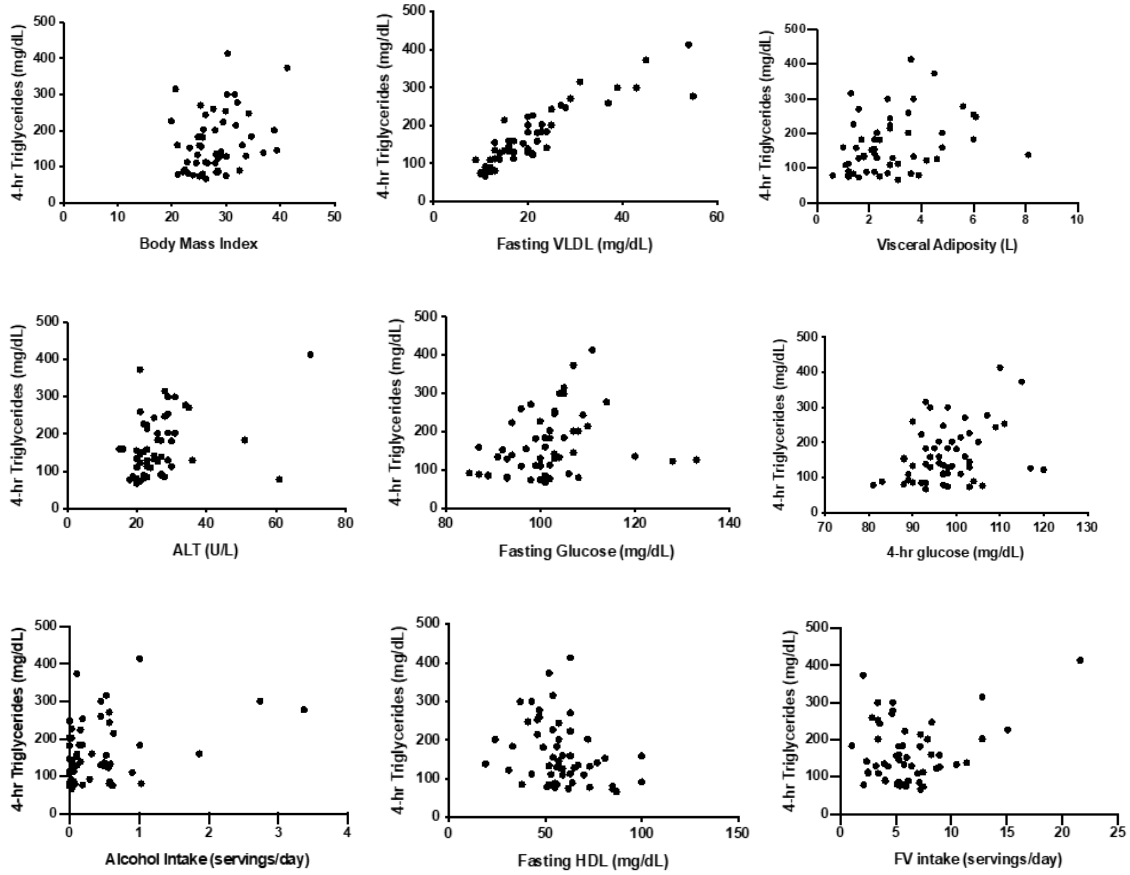

Figure 3. Scatter plots of variables significantly associated with postprandial triglycerides.

Variables Stratified by 4-hour Triglyceride Concentrations

Participants were divided into quartiles based on 4-hour TG concentrations in order to determine differences in lifestyle variables or risk factors as TG increase (**Table 4)**. Overall, across all participants 4-hour triglycerides ranged from 67 to 414 mg/dL. VLDL was the only variable observed to significantly increase across quartiles of 4-hour TGs (p

< 0.0001). No other metabolic concentrations, lifestyle variables, or risk factors were significantly different across quartiles (ps > 0.05).

Table 4. Lifestyle and risk factor variables stratified by 4-hour TG concentrations.

	Q1	Q2	Q3	Q4	p-value
4-hour TG (mg/dL)	81.5 ± 7.2	124.1 ± 10.6	172.6 ± 21.3	280 ± 57.2	<0.0001
BMI (kg/m^2)	26 ± 3.4	28.3 ± 3.6	28.5 ± 5.8	28.7 ± 5.8	0.43
Body Fat (%)	36.39 ± 8.5	35.59 ± 8.4	41.5 ± 8.5	35 ± 8.2	0.18
Fat Free Mass (%)	63.4 ± 8.2	64.4 ± 8.4	58.6 ± 8.5	65 ± 8.2	0.18
Systolic BP (mmHg)	121.5 ± 16.9	132.2 ± 16.4	136.1 ± 24.6	133.2 ± 14.4	0.20
Diastolic BP (mmHg)	77.4 ± 10.8	83.1 ± 9.6	82.9 ± 18.5	85.3 ± 9.8	0.09
VAT (L)	2.1 ± 1	3.0 ± 1.8	2.8 ± 1.5	3.5 ± 1.6	0.12
Total-C (mg/dL)	170.5 ± 44.3	165.9 ± 32.9	181.2 ± 37.4	182.3 ± 20.1	0.51
LDL-C (mg/dL)	91.8 ± 33.4	95.3 ± 25.8	99 ± 30.4	97.4 ± 20.4	0.92
HDL-C (mg/dL)	66.4 ± 18.	54.8 ± 15	59.9 ± 19.1	52.2 ± 9.5	0.10
VLDL-C (mg/dL)	11.4 ± 1.0^{a}	15.9 ± 3.7^{ad}	20.3 ± 3.7^{bd}	32.4 ± 12.7^{c}	<0.0001
Fasting Glucose (mg/dL)	96.3 ± 7.5	104.5 ± 13	100.9 ± 5.8	104.1 ± 5.6	0.05
4-hour Glucose (mg/dL)	93.6 ± 7.8	99.5 ± 8.9	96.6 ± 5.1	101.6 ± 7.9	0.09
ALT (U/L)	25.2 ± 11.2	24.6 ± 4.7	25.9 ± 8.7	29.9 ± 12.0	0.09
FMD (%)	4.7 ± 2.0	4.4 ± 1.7	3.4 ± 1.7	3.5 ± 1.2	0.25
Past Week MET-minutes	4776 ± 4390	4628 ± 4011	4412 ± 4608	4535 ± 3565	0.92
Past Year MET-hours	7178 ± 2604	5662 ± 3360	6893 ± 4572	6045 ± 3015	0.37
Lifetime MET-hours	186379 ± 121614	199946 ± 184496	193629 ± 156465	208577 ± 134578	0.89
Accelerometer, Steps/day	11241 ± 3119	10920 ± 2631	9283 ± 2980	10556 ± 2790	0.31
Accelerometer, MVPA/day	179.8 ± 72.1	161.7 ± 53.4	146.4 ± 54.6	163 ± 43.9	0.79
FV Intake (frequency/day)	5.5 ± 1.5	6.1 ± 3	6.0 ± 2.9	7 ± 5.5	0.97
SSB Intake (frequency/day)	0.4 ± 0.4	0.8 ± 1.1	0.7 ± 0.9	0.4 ± 0.4	0.76
Meat Intake (frequency/day)	1.6 ± 0.9	1.7 ± 1.2	1.7 ± 1.3	2.0 ± 2.0	0.92
Whole Grain Intake (% grains)	21.2 ± 11.5	33.8 ± 14.6	33.9 ± 25.4	25.0± 12.8	0.13
Alcohol Intake (frequency/day)	03 ± 0.3	0.34 ± 0.3	0.3 ± 0.5	0.9 ± 1.1	0.09

Statistical results for each variable represent findings of a one-way ANOVA or Kruskal-Wallis test. Data are represented as Mean ± SD. Superscript letters demonstrate results of post hoc comparisons. Within a row, cells with similar superscript letters do not differ. TG, triglycerides; BMI, body mass index; BP, blood pressure; VAT, visceral adipose tissue; Total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol, VLDL-C, very-low-density lipoprotein cholesterol; ALT, alanine aminotransferase; FMD, flow-mediated dilation; MET, metabolic

equivalents; MVPA, moderate-vigorous physical activity minutes; FV, fruit and vegetable; SSB, sugar-sweetened beverage.

Regression Analyses

Regression analyses were performed to determine the strongest predictors of PPL. A linear regression (Enter method, **Table 5**), with 4-hour TGs as the dependent variable, was performed using independent variables that were observed to be significantly correlated with 4-hour TGs: BMI, visceral adiposity, postprandial glucose, ALT, FMD, fruit and vegetable intake, and alcohol intake. Fasting glucose and body mass were not included since they were highly correlated and physiologically related with postprandial glucose and BMI, respectively. The full model, which included all aforementioned variables, significantly predicted 4-hour triglycerides ($p = 0.002$) with an R^2 value of 0.37. Among all contributing variables, however, ALT was the only significant predictor ($p = 0.03$).

To simplify the regression model to only include the most influential independent variables, a second linear regression was performed using the Backward Elimination method (**Table 6**). Backward Elimination regression conducts multiple analyses and at each stage removes the variable with the largest p-value, as long as it is greater than $p = 0.10$. This is repeated until all remaining variables have a $p < 0.10$. This approach can determine which variables used in the full model were the most significant predictors of 4-hour TGs. Postprandial glucose ($p = 0.01$), ALT ($p = 0.007$), and alcohol intake ($p = 0.04$) were the strongest predictors and were retained in the final model. The final simplified model significantly predicted 4-hour TGs ($R^2 = 0.31$; $p = 0.000$). The change in R^2 from the full model to the backward eliminated model was -0.06.

Table 5. Results of linear regression with enter method.

	R^2	Standardized β coefficient	P value
Full Model	0.37		0.002
BMI		0.181	0.26
VAT		-0.007	0.97
Postprandial glucose		0.224	0.09
ALT		0.292	0.03
FMD		-0.096	0.46
FV intake		0.178	0.16
Alcohol intake		0.223	0.07

Table 6. Results of linear regression with backward elimination method.

	R^2	Standardized β coefficient	P value
Backward Eliminated Model	0.31		0.000
Postprandial glucose		0.308	0.01
ALT		0.330	0.007
Alcohol intake		0.248	0.04

CHAPTER V

DISCUSSION

Summary of Main Findings

The purpose of this study was to determine how aging influences the postprandial TG response, and which variables are most predictive of postprandial TG concentrations. We found that specific decades of aging were not predictive of the 4-hour TG response. Across groups, no age strata appeared to be more susceptible to PPL. Additionally, while we observed some differences in physical activity level across groups, such as average MVPA minutes/day, no physical activity variable that we measured was significantly predictive of 4-hour TGs. However, our results showed that numerous variables were associated with 4-hour TGs, including BMI, visceral adiposity, fasting VLDL, fasting HDL, ALT, fruit and vegetable intake, and alcohol intake. After regression analyses were performed, ALT, postprandial glucose, and alcohol intake appeared to be the most predictive of postprandial TGs within our target age groups. Thus, this cross-sectional study advances knowledge regarding determinants of PPL in aging adults.

Impact of Aging

While age is a known risk factor for development of CVD, this study did not observe an independent association between age and 4-hour TGs in our sample of adults aged 50-89 years. This is an interesting finding, since it has been demonstrated that older

adults tend to experience greater PPL than younger adults (Katsanos, 2014). Previous theories have been postulated as to why older adults might be more susceptible to PPL than their younger counterparts. Aging adults tend to exhibit loss of muscle mass (sarcopenia), which will lead to a reduction in LPL activity, which could precipitate decreased uptake of TGs (Katsanos, 2014). Reductions in muscle LPL activity has been shown in older adults (Bey, Areiquat, Sano, & Hamilton, 2001), which when combined with sedentary activity (Zderic and Hamilton, 2006), can further exaggerate these differences, especially within the postprandial state. This study sought to determine if there is a direct link between age and PPL within this context of declining metabolic function. While there are clear differences between young, active individuals and the aging population (Bernstein and Munoz, 2012; Katsanos, 2014), it is possible that detectable differences in postprandial TGs do not exist within the decades of aging that we studied, especially when considering that our groups had little variation in body composition.

Impact of Physical Activity

Furthermore, physical activity variables we measured did not coincide with postprandial TGs. Acute exercise has been previously shown to modify the postprandial response (Gill and Hardman, 2000). Likewise, chronic physical activity can result in better postprandial TG concentrations (Miller et al., 2011). Therefore, there is a clear connection between physical activity and the postprandial TG response. Based on what is currently known about aging and muscle loss, it is reasonable to speculate that being physically active during aging can potentially combat the detrimental effects of sarcopenia, and by association, could also positively influence lipid metabolism as a

mechanism of improvement in cardiovascular health (Volpi, Nazemi, and Fujita, 2004). Physical activity can lead to substantial improvements in visceral adiposity, glucose tolerance, and fat mass (Warburton, Nicol, and Bredin, 2006), which could indirectly affect postprandial lipemia. In our study, there were no significant differences between age groups with regard to body mass, visceral adiposity, or fat free mass %, nor were there widespread differences in activity level. Given these null differences between age strata, it is understandable that we did not observed differences in postprandial TG between groups.

Few studies have investigated postprandial metabolic responses between young adults and older adults according to physical activity level. Emerson et al. (2018) found that chronic physical activity, independent of acute exercise, can lessen the postprandial response in older active adults when compared to older inactive adults. That study also found that younger active adults demonstrated the most favorable TG response over both older age groups, suggesting that age and physical activity level are independent determinants of PPL. On the other hand, Koemel et al. (2020) observed similar responses between younger and older active adults, as well as younger and older inactive adults, suggesting that physical activity level was more influential than aging in determining postprandial TG. While both of these studies demonstrate that both age and physical activity have clear effects on PPL, it is important to note that both studies compared younger adults (age 18-35 years) with older adults (age >60 years). The present study looked at individuals evenly distributed between ages 50-89 years. Differences in physical activity indices across this aging spectrum might be less apparent than comparing younger and older adults.

Factors Predictive of Postprandial Triglycerides

Although numerous variables were associated with postprandial TGs, our findings suggest that the most predictive variables were ALT, postprandial glucose, and alcohol intake. Alcohol intake was observed to be the most influential dietary variable on the postprandial TG response. Alcohol, which is metabolized in the liver and classified as a hepatotoxin, can lead to decreased oxidation of fatty acids and, thus, accumulation of TGs in excess (Mahan and Raymond, 2017). Furthermore, chronic alcohol abuse is commonly documented in individuals with severe hypertriglyceridemia (Bessembinders, Wielders, and de Weil, 2010). The acute effect of alcohol on postprandial TGs has been documented to some extent as well. Alcohol, regardless of type, appears to substantially raise the postprandial TG response when compared to other drinks, such as water or juice when combined with a meal (Bozzetto, Pepa, Vetrani, and Rivellese, 2020). It is thought that acute alcohol consumption can increase endogenous VLDL synthesis in the liver, as well as downregulate LPL activity, which could explain the increase in TGs (Dias et al., 2017). To our knowledge, this study is the first to demonstrate a correlation between regular alcohol consumption and postprandial TGs in a sample of older adults. However, it should be noted that most participants in our sample were consuming less than 1 alcoholic beverage per day. Overall, our data is consistent with previous research regarding a connection between alcohol intake and TG concentrations.

Alanine aminotransferase (ALT), a liver enzyme involved in amino acid metabolism and gluconeogenesis, is often used as an indicator of liver fat accumulation and has been associated with non-alcoholic fatty liver disease (NAFLD) (Schindhelm et

al, 2006). NAFLD, which affects approximately 25% of the adult population, is mechanistically linked with development of CVD (Kasper et al, 2020). Fat accumulation in the liver, especially when compounded with increased visceral adipose tissue, leads to increased hepatic de novo lipogenesis, which can contribute to dyslipidemia through excess secretion of VLDL-cholesterol (Kasper et al, 2020). Additional alterations in lipoproteins such as reduced HDL-cholesterol and accumulation of small, dense LDL-cholesterol will increase the body's susceptibility to oxidation and atherogenesis (Kasper et al, 2020). Furthermore, one prospective cohort study found that in individuals between the ages of 50-75 years, elevated ALT was significantly associated with coronary heart disease events after 10 years of follow-up, independent of other risk factors (Schindhelm et al, 2006). Although a liver biopsy is considered the gold standard for diagnosis of NAFLD, this is rarely feasible in a research setting, therefore ALT is a common measure used in research and clinically to test for liver steatosis. Although an imperfect proxy, elevated ALT concentrations can potentially indicate liver fat accumulation. Likewise, there is a clear connection between NAFLD and abnormal lipid profiles. Studies that have administered a high-fat meal to individuals with fatty liver have markedly raised postprandial TG concentrations over controls (Schindhelm, Diamant, and Heine, 2007). In one study, serum TGs were raised in 67% of ultrasound-confirmed NAFLD cases (Mahaling, Basavaraj, and Bika, 2013). Therefore, our finding of ALT as a significant determinant of postprandial TGs agrees with previous data regarding liver steatosis and dyslipidemia.

Elevated postprandial glucose was another significant predictor of 4-hour TGs in the final regression model. Elevated postprandial glucose is potentially indicative of

insulin resistance and impaired glucose tolerance. Insulin resistance is associated with both obesity and NAFLD (Gaggini et al., 2013). Under normal conditions, insulin inhibits lipolysis, or the breakdown of fat to be used for energy. When there is increasing insulin resistance, this pathway becomes resistant to inhibition, increasing the release of free fatty acids even in the presence of insulin, which will ultimately promote triglyceride synthesis in the liver (Gaggini, et al., 2013). Previous studies have demonstrated that individuals with NAFLD have increased hepatic insulin resistance as well, which can lead to the overproduction of VLDL (Meshkani and Adeli, 2009). This combination of altered metabolic function, especially when put under stress following administration of a high fat meal, at least partially explains the elevated postprandial TG response.

Additionally, the connection between insulin resistance and PPL has been previously documented. In individuals newly diagnosed with type 2 diabetes, an oral fat load test resulted in greater postprandial TGs than individuals with normal glucose tolerance (Madhu et al., 2008). It is plausible that PPL is a common metabolic abnormality of diabetes, and could further establish the connection between diabetes and CVD. This connection is significant within our population, considering that over half of individuals exhibited fasting glucose concentrations indicative of pre-diabetes (>100 mg/dL). However, it is important to note that the meal we administered was not meant to measure glucose tolerance, as it was only 26% carbohydrate, and postprandial glucose concentrations were measured at 4 hours, which is different than the standardized oral glucose tolerance test (2 hours).

Growing evidence continues to support that the presence of insulin resistance, liver fat accumulation, and elevated ALT possess enough metabolic significance to serve

as early screening tools for more severe chronic diseases such as NAFLD and CVD. One study postulated that the triglyceride and glucose index (TyG), or the product of both TG and glucose values, which already serves as a marker of insulin resistance, could also be used to assess risk for NAFLD (Zhang, et al., 2017). In this study by Zang et al., 72.8% of individuals had NAFLD in the highest quartile of TyG compared to only 11.6% in quartile 1 (Zhang, et al., 2017). Furthermore, 66.2% of individuals in the highest quartile also had elevated ALT compared to 17.8% in quartile 1 (Zhang, et al., 2017). The present study found that both ALT and impaired glucose tolerance were significant predictors of 4-hour TGs in all age groups, which supports to the notion that presence of PPL could serve as an early indicator of declining metabolic function.

Flow-Mediated Dilation

There were no significant differences in FMD across age groups in our study. Although the highest FMD responses were seen in the youngest age group, average FMD across all groups ranged between 3.5-4.7%, which appears to be similar to other study averages of similar age groups (Yeboah et al., 2007; Atkinson and Batterham, 2013). A meta-analysis of FMD on CVD risk prediction estimates that a 1% higher FMD is associated with a 10% reduction in CVD-related events (RR: 0.90; CI: 0.86-0.94) (Ras et al., 2013).

A decrease in physical activity during aging will decrease NO expression and upregulate pro-inflammatory pathways, which will amplify endothelial dysfunction (Francescomarino et al., 2009). In our study, total steps/day was positively associated with FMD, suggestive that level of acute physical activity could have influenced FMD response and improved endothelial function. However, this was not consistent across all

physical activity variables that we measured. Koemel et al. (2020) found that younger active adults had significantly higher FMD percentages than older inactive adults. However, the same study also did not find any differences between older active and older inactive adults, despite differences in triglyceride concentrations (Koemel et al., 2020). This data is consistent with the present study's findings. It is feasible that in our sample, the differences between groups were less pronounced, since we focused entirely within the older adult population. Celermajer et. al. (1994) found that FMD starts to decline by age 40 in men, so it is possible that age-related declines in endothelial function occurred prior to the four decades we assessed.

Strengths and Limitations

There are several strengths and limitations to this study. The participants were equally distributed across age groups with an even number of males and females. Participants were not excluded based on chronic disease presence or medication use, which allowed for greater external application, and a more accurate representation of older adults. Physical activity was assessed via five different methods, and we estimated both acute and chronic physical activity levels. Postprandial metabolic data were derived from an abbreviated fat tolerance test, which allows for the participant to leave the lab for a significant period of time. This provides increased flexibility and ease of participation for individuals.

However, estimates of lifetime physical activity could be potentially influenced by recall bias when estimating activity retrospectively at different stages in life. Further, a more precise measure of glucose control would have been ideal, such as HbA1c or insulin, so that we could have better inferred long-term glucose control or insulin

sensitivity (e.g. calculating HOMA-IR). While the participants were instructed not to eat anything or engage in any physical activity during that 4-hour period, participants were not overtly monitored. Finally, participants in the older groups may not be as representative of the general population due to selection bias. Older adults within the 70s and 80s groups were primarily active individuals able to maintain a significant level of independence. Individuals at that age experiencing a decline in health and potentially requiring living assistance may not have feasibly been able to complete the tasks required for participation.

Recent Covid-19 restrictions resulted in significant difficulties in recruiting the older population, which is reflected in the total participant count, particularly within the 80s group. Major recruitment methods for this population, including announcements in nursing homes and assisted living facilities, were unable to occur after February 2020. Considering that older adults are considered a high-risk population for Covid-related complications, a conservative approach to recruitment was necessary to ensure this population did not experience increased risk of virus transmission.

Conclusion and Future Directions

In conclusion, this study did not observe clear variations in postprandial TGs according to age or physical activity level alone. We did identify several variables associated with 4-hour triglycerides. While age is a non-modifiable risk factor for chronic disease, it should be evaluated within the context of other risk factors. Even though our data did not present a marked change in fasting or postprandial TGs as age increases, this does not mean no metabolic differences exist. Aging encompasses a complex physiological state, which is influenced by both endogenous and exogenous factors.

Many dietary and physical activity variables we assessed were not significant across age groups, which could explain why no differences were found in the triglyceride response between age groups.

The three most predictive variables within our target population were ALT, postprandial glucose, and alcohol intake. These variables are particularly relevant within the older adult population since they are more susceptible to fatty liver and increasing insulin resistance. Future research should investigate the relationship between ALT and PPL, the prevalence of insulin resistance in individuals who experience an exaggerated triglyceride response, and the effect of chronic alcohol consumption within the older adult population to better understand its role in lipid metabolism.

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