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# The Effects of Walking on Serum Lipids and Lipoproteins in Over-weight and Obese Women: A Systematic Review and Meta-Analysis

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**ACCEPTANCE**

This dissertation, THE EFFECTS OF WALKING ON SERUM LIPIDS AND LIPOPROTEINS IN OVERWEIGHT AND OBESE WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS, by ANJULYN M. BALLARD, was prepared under the direction of the candidate's Dissertation Advisory Committee. It is accepted by the committee members in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the College of Education & Human Development, Georgia State University.

The Dissertation Advisory Committee and the student's Department Chairperson, as representatives of the faculty, certify that this dissertation has met all standards of excellence and scholarship as determined by the faculty.

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# THE EFFECTS OF WALKING ON SERUM LIPIDS AND LIPOPROTEINS IN OVER-WEIGHT AND OBESE WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS

by

ANJULYN M. BALLARD

Under the Direction of Dr. Walter R. Thompson

ABSTRACT

67 % of women are overweight and obese. Overweight and obese individuals have more diagnoses of dyslipidemia than normal weight adults. Dyslipidemia often leads to atherosclerosis, and women who are overweight and obese are at an increased risk of developing atherosclerosis and experiencing stroke or heart failure. Walking is generally considered a safe exercise and can be beneficial for cardiovascular health. However, for overweight and obese women, the effects of walking on serum lipids and lipoproteins have demonstrated mixed results in interventions that are not focused on weight-loss. The purpose of this systematic review and meta-analysis was to determine if exclusive walking has a significant effect on serum lipids and lipoproteins in overweight and obese women. Meta-analyses of 22 exclusive walking interventions [$N$ =1,206; median age = 47 years; median body mass index (BMI) = 28.40 kg/m$^2$] demonstrated that walking can improve total cholesterol [raw mean difference (RMD) = 6.67 mg/dL, $p$ = .04] and low-density lipoproteins (RMD = 7.38 mg/dL, $p$ = .04). Walking reduces total cholesterol and low-density lipoproteins in overweight and obese women exclusive of diet and weight-loss, and the findings from this meta-analysis supports promotion of walking as an exercise therapy.

INDEX WORDS: Raw Mean Difference (RMD), Total Cholesterol, Triglycerides, High-Density Lipoproteins, Low-Density Lipoproteins, Overweight, Obese

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ANJULYN M. BALLARD

A Dissertation

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in

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## DEDICATION

This dissertation is dedicated to my mother and father (posthumously), who have always believed in me, and who have loved me unconditionally. Also, this dissertation is dedicated to my son, who I love dearly and who has given me a fulfilling life as a mother, and to my close family and friends for their support and encouragement.

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## Introduction

Overweight and obesity are major public health disorders in the United States [Center for Disease Control and Prevention (CDC), 2017a]. 26.5 % of women are overweight, and 66.6 % of women (about 2 in 3) are overweight or obese [U.S. Department of Health and Human Services (HHS), 2017b]. Data from the 2015 to 2016 National Health and Nutrition Examination Survey (NHANES) indicates 41.1% of women are obese, and 9.7% of women are severely obese (Hales, Fryar, Carroll, Freedman, & Ogden, 2018). Overweight is defined as having a body mass index (BMI) between 25 kg/m$^2$ and 30 kg/m$^2$ (CDC, 2016), obese is having a BMI of 30 kg/m$^2$ or higher, and severely obese is a BMI of 40 kg/m$^2$ or higher (Hales et al., 2018). Overweight and obesity are risk factors for cardiovascular disease (CDC, 2017a). However, they are risk factors that are be controlled through diet and regular exercise. Walking interventions, for example, for overweight and obese women have demonstrated improved lipids, but lipids outcomes appear to be moderated by walking intensity, duration, and weight-loss (Ard et al., 2017, Mezghanni et al., 2014). A collective analysis of walking interventions for this population will determine its effects on lipids, and if intensity, duration, and weight-loss significantly moderate lipid outcomes.

Obesity significantly increased in men and women between the years of 1980 and 2000 (Flegal, Kruszon-Moran, Carroll, Fryar, Ogden, 2016). Between 2005 and 2014, the prevalence of overall obesity and extreme obesity significantly increased in women, but there were no additional increases in men (Fryar, Carroll, Ogden, 2016). The body mass-mortality association is higher for women than for men. For overweight and obese women, there are increasing trends in mortality rates, but for men mortality rates increase for the severely obese (Yu, 2016). Not only are overweight and obesity a serious health disorder and disease for women, they poses a greater risk of mortality.

Overweight and obese individuals have a higher incident rate of dyslipidemia than normal weight adults (Saydah et al., 2014). The prevalence of dyslipidemia has been highest among obese adults, followed by overweight, and normal weight adults (Saydah et al., 2014; Table 1).

Table 1

*Incident Rate of Dyslipidemia*

| | 1999-2002 | 2003-2006 | 2007-2010 |
|---|---|---|---|
| Obese | 50.7 (48.4, 53.0) | 48.7 (46.2, 51.2) | 49.74 (47.4, 52.0) |
| Overweight | 47.6 (45.6, 49.7) | 45.8 (43.2, 48.3) | 44.2 (42.5, 46.0) |
| Normal Weight | 29.4 (27.8, 31.0) | 26.8 (24.7, 29.0) | 28.6 (27.2, 30.0) |

*Saydah, et al., 2014*

Dyslipidemia is characterized by an abnormal level of serum lipids and lipoproteins (CDC, 2015a). It can lead to a build-up of plaque in the arterial walls, resulting in narrowing of the arteries [World Health Organization (WHO), 2017]. Narrowing of the arteries decreases

blood flow, which is a process known as atherosclerosis (CDC, 2015b). Atherosclerosis is a cardiovascular disease (CVD) that can lead to a weakening of the myocardium over time, and may ultimately result in heart failure (Braunwald, 2015). In addition, atherosclerosis can lead to cerebrovascular disease (CBD), resulting in an ischemic stroke (CDC, 2018a). Ischemic stroke is caused by severely reduced blood flow to the brain, potentially resulting in complications such as brain edema, pneumonia, clinical depression, and seizures. Followed by smoking, dyslipidemia has been reported as the highest risk factor for atherosclerosis-related disorders (reduced blood flow to the brain and heart), and individuals with dyslipidemia are three times more likely to experience signs and symptoms of CBD and CVD than individuals with normal lipids (Kastorini et al., 2013). Because incidents of dyslipidemia are higher in overweight and obese adults, women who are overweight and obese are at an increased risk of developing atherosclerosis and experiencing a stroke or heart failure.

Stroke is the third leading cause of death, and one in five women in the U.S. experience a stroke [National Stroke Association (NSA), 2018]. Stroke kills twice as many women as breast cancer, and the risks of stroke for women are higher than for men as women can experience symptoms that are not typically recognized as stroke symptoms (e.g., nausea or vomiting, hiccups, general weakness), often resulting in delayed treatment (NSA, 2018). Heart disease is the leading cause of death for women in the U.S. and in 2013, nearly three million women died from heart disease accounting for about one in every four deaths (CDC, 2017e). Women are also more likely than men to have heart attack symptoms that are unrelated to chest pain (e.g., abdominal discomfort, unusual fatigue, dizziness, nausea), increasing the risk of sudden death [CDC, 2018c;

American Heart Association (AHA), 2018a]. Also, heart disease costs the U.S. about $200 billion per year, which includes costs for health care services, medications, and lost productivity (CDC, 2017b).

Family history, sex, race, and age are risk factors for CVD (AHA, 2018b). Post-menopausal women are at increased risk of CVD due to a decline in endogenous estrogen as it has demonstrated a protective effect against atherosclerosis (Papakonstantinou, Stamou, Baikoussis, Goudevenos, & Apostolakis, 2013). However, diabetes, high blood pressure, diet, alcohol consumption, tobacco use, high total cholesterol, overweight and obesity, and physical inactivity are other risk factors of CVD that are generally controllable by not smoking, consuming a healthy-balanced diet, and participating in regular physical activity.

Physical inactivity is a result of not engaging in the recommended amount of regular physical activity as prescribed by the U.S. Department of Health and Human Services (HHS). Per the 2008 Physical Activity Guidelines for adults, HHS recommends at least 150 minutes of moderate-intensity aerobic physical activity each week (HHS, 2008). However, only one in three adults get the recommended amount of physical activity each week (HHS, 2018a). For women, more than 60% do not participate in the recommended amount of physical activity, more than 25% are completely inactive, and physical inactivity is more common among women than men (CDC, 2018b). Physical activity increases cardiorespiratory fitness, and cardiorespiratory fitness provides protective benefits as it reduces the risk of CVD (Gander et al., 2015). Also, moderate to high levels of cardiorespiratory fitness have attenuated the effects of dyslipidemia on CVD mortality (Farrell et al., 2017). In addition, cardiorespiratory fitness has attenuated the adverse effects of excess adiposity and other CVD risk factors, such as hypertension, metabolic syndrome, and type 2 (T2D) diabetes that have been associated with obesity (Oktay et al., 2017).

Being overweight or obese increases the risk of CVD because they are linked to other risk factors such as hypertension, diabetes, and hypercholesterolemia and elevated triglycerides (National Heart, Lung, and Blood Institute, 2014). High total cholesterol, triglycerides, and abnormal lipoproteins have been directly related to CVD, but they can be controlled through diet, weight-management, and physical activity. High total cholesterol is 200 mg/dL of blood or higher, high triglycerides is 150 mg/dL of blood or higher, and abnormal lipoproteins are low-density lipoproteins (LDLs) of 100 mg/dL of blood or higher and/or high-density lipoproteins (HDLs) that are less than 60 mg/dL of blood (CDC, 2015a). LDLs contribute to atherosclerotic plaque build-up in the arteries, but HDLs can transport LDLs away from the arteries and back to the liver, where they are metabolized and eliminated as waste.

95 million adults aged 20 years and older have high cholesterol, and the risk of heart disease is doubled with this condition. Also, 37 % of adults have high LDLs, but only one-third of adults have this condition under control (CDC, 2015a). Finally, 36.5% to 43.4 % of women have high cholesterol, with non-Hispanic Whites having the highest percentage (43.4%) (CDC, 2017c). High cholesterol, triglycerides, and LDLs are detrimental because of their direct relationship to CVD. However, for women aged 55 years and older, having more than one risk factor further increases the risk of developing heart disease as a result of menopause (HHS, 2017a). Regular exercise provides several health benefits, primarily for cardiovascular health (Oktay et al., 2017). Having a lifestyle that includes regular exercise can aid in eliminating other risk factors (overweight and obesity, high cholesterol and LDLs, high blood pressure) and reduces mortality (Farrell et al., 2017; Gander et al., 2015; Oktay et al., 2017).

Walking has demonstrated beneficial effects for overall health (Baker, Milner, & Campbell, 2015; Mezghanni et al., 2014). Weight-loss, improved body composition, cardiorespiratory

health, and cardio-metabolic health care benefits of walking as regular exercise (Gieck & Olsen, 2007; Haines et al., 2007; Schulz et al., 2015). Walking interventions and a holistic health program (program focused on improving physical, emotional, spiritual, social, occupational, and intellectual wellness; Gieck & Olsen, 2007) have demonstrated reductions in waist circumference and BMI in overweight and obese women (Gieck & Olsen, 2007; Haines et al., 2007; Schulz et al., 2015). Participants also experienced an increase in muscle mass, and a decrease in fat mass (Gieck & Olsen, 2007). They also experienced decreased blood pressure (Schulz et al., 2015), improved blood glucose, triglycerides, and total cholesterol (Haines et al., 2007; Schulz et al., 2015). Walking, for regular exercise, improves overall health and it is effective for eliminating other CVD disease risk factors (excess weight, elevated blood glucose, hypercholesterolemia, and elevated triglycerides). However, for overweight and obese adults, particularly women, studies that investigated the effect of walking on lipids have demonstrated mixed results (Buyukyazi, 2008; Mezghanni et al., 2014; Vega-López et al., 2015; Wooten et al., 2011). Weight-status is an important factor to consider because walking interventions with overweight and obese women do not consistently demonstrate improvement in total cholesterol, triglycerides, HDLs, and LDLs. Baseline lipids (normal versus abnormal), walking intensity, and duration of the intervention are variables that appear to moderate lipid outcomes in overweight and obese women (Buyukyazi, 2008; Mezghanni et al., 2014; Vega-López et al., 2015; Wooten, Biggerstaff, & Ben-Ezra, 2011).

In these experiments, the studies primarily focused on changes in lipids, however diet and weight-loss were not used as variables to determine lipid outcomes. In weight-loss focused interventions, diet or diet and physical activity are used to assess changes in weight, body composition, lipids, and other cardiovascular indicators of health (e.g., blood pressure); and improved lipids with significant weight-loss have been consistent observations (Ard et al., 2017; Harrison,

Mattson, Durbin, Fish, & Bachman, 2012; Rock, Flatt, Barkai, Pakiz, & Heath, 2017; Ruiz, Ortega, & Labayen, 2013; Zinn et al., 2017). However, in interventions that are not focused on weight-loss, observation of improved lipids are less consistent (Buyukyazi, 2008; Mezghanni et al., 2014; Vega-López et al., 2015; Wooten et al., 2011), and total cholesterol, LDLs, and triglycerides are mostly improved under moderate to vigorous or vigorous intensity exercise (Buyukyazi, 2008; Mezghanni et al., 2014).

It has been widely accepted that cardiorespiratory fitness (CRF) is attainable and beneficial for overweight and obese adults. An inverse relationship between CRF and mortality has been exhibited (Lavie et al., 2013), as well as an inverse relationship between physical activity, adiposity, and arterial stiffness (Ananey et al., 2015). Also, a similar mortality risk for cardiorespiratory-fit obese adults and cardiorespiratory-fit normal-weight adults has been demonstrated (Barry et al., 2014; McAuley, Kokkinos, Oliveira, Emerson, & Myers, 2010; McAuley, Smith, Emerson, & Myers, 2012; Vranian et al., 2013). However, it is also important to know if a simple and safe aerobic exercise for this population, such as walking, has significant implications for cardiovascular health regarding improving lipids to prevent the development of atherosclerosis. A systematic review and meta-analysis will provide a collective evaluation of all identified interventions that have used walking to test changes in lipids of overweight and obese women.

A systematic review collates all possible experimental studies that meet the study's inclusion criteria to address a research question. Inclusion criteria, for example, may be experiment/control design, a specific age range, or studies that focus on a defined health condition. A systematic review synthesizes characteristics and findings of independent studies using a method that is designed to minimize bias. A meta-analysis summarizes the results of these independent

studies, and it statistically provides more precise estimates of treatment effects, than those obtained from independent studies included within a review (Borenstein, Hedges, Higgins, & Rothstein, 2009; Higgins & Green, 2011). Similar systematic reviews and meta-analyses related to the effects of exercise on lipids have been previously completed. However, the studies either examined the effects of aerobic exercise (in general) on lipids and lipoproteins (Asikainen, Kukkonen-Harjula, & Miilunpalo, 2004; Kelley, G. A., Kelley, K. S., & Vu Tran, 2005; Koba et al., 2011), or they specifically examined the effects of walking on lipids and lipoproteins, but the samples were not limited to overweight and obese women (Hanson & Jones, 2015; Kelley, G. A., Kelley, K. S., & Tran, 2004). In addition, none of the studies investigated the effects of aerobic or walking intensity (moderate and vigorous) on lipids or lipoproteins. However, all of the systematic reviews and meta-analyses concluded that aerobic exercise (Asikainen et al., 2004; Kelley et al., 2005; Koba et al., 2011) or walking (Fogelholm, 2005; Hanson & Jones, 2015; Kelly et al., 2004) improves lipids and lipoproteins, and one meta-analysis resulted in showing that walking increases HDLs, decreases LDLs and total cholesterol, and was independent of changes in body composition in overweight and obese adults (Kelley, G. A., Kelley, K. S., & Tran, 2004). However, Kelley et al. (2004) did not investigate changes in lipids in relation to walking intensity, and the investigation did not exclusively focus on overweight and obese women. Because 66.6 % of women are overweight or obese (HHS, 2017b), CVD is the leading cause of death in women, and women are more likely to suddenly die from CVD than men, completing a systematic review and meta-analysis focused on walking and walking intensities will determine treatment effectiveness for improving lipids.

## Literature Review

Being overweight increases the risk of developing not only dyslipidemia, but also hypertension, heart disease and stroke, T2D, cancer, non-alcoholic fatty liver disease, gallbladder disease, kidney disease, sleep apnea, osteoarthritis, clinical depression and anxiety, and low quality of life (CDC, 2015d). However, being obese further increases the risk of developing these associated health disorders and diseases (CDC, 2015d).

When weight-gain occurs, adipocytes undergo hypertrophy, hyperplasia, and remodeling that leads to the proliferation of inflammatory cells (Kernan, Inzucchi, Sawan, Macko, & Furie, 2013; Quail & Dannenberg, 2019; Włodarczyk & Nowicka, 2019). In healthy adipose tissue, the pro-inflammatory response of immune cells has been shown to be essential for expansion and remodeling (Blüher, 2016). However, when adipose tissue must excessively expand and remodel, necrosis occurs, and this inflammatory response triggers the production and release of several adipokines (inflammatory cytokines) into the adipocyte microenvironment (Quail & Dannenberg, 2019). The bioactivity of inflammatory cytokines such as leptin, adiponectin, tumor necrosis factor alpha (TNF-α), interferon gamma (IFNγ), interleukin 1 beta (IL-1β), and interleukin 6 (IL-6) have been widely investigated in chronic diseases that are related to overweight and obesity (Quail & Dannenberg, 2019; Sletten, Peterson, & Schaffer, 2018). The production and release of these cytokines leads to oxidative stress, which is the pathology behind obesity-associated chronic diseases and related health conditions (Lysaght et al., 2011; Włodarczyk & Nowicka, 2019).

Oxidative stress is an imbalance of reactive oxygen species (ROS) and antioxidants (Włodarczyk & Nowicka, 2019). Antioxidants are compounds that counteract or neutralize the harmful effects of ROS. ROS are unstable cellular molecules (free radicals) that react with other

cellular molecules. Increased ROS induces endogenous damage to DNA, transcription interruption, and cell-cycle arrest (Włodarczyk & Nowicka, 2019). The imbalance of ROS and antioxidants cause oxidative damage to lipids, proteins, and nucleic acids; and this oxidative damage leads to dysregulation of the following hormones: insulin-like growth factor 1 (IGF-1), insulin, adiponectin, and leptin (Crujeiras, Díaz-Lagares, Carreira, Amil, & Casanueva, 2013; Orrù et al., 2017). Dysregulation of these hormones primarily contribute to the etiology of atherosclerosis, diabetes, cancer, and neurodegenerative disease (Crujeiras et al., 2013). These diseases are serious health disorders that reduce quality of life and increase mortality; but because obesity is a controllable risk factor, the risk of developing obesity-related health disorders can be controlled through weight-management and healthy lifestyle habits.

Hypertension, heart disease, stroke, T2D, and cancer are major health disorders that have been associate with obesity, and they present as multi-morbidities in obese individuals (Agborsangaya, Ngwakongnwi, Lahtinen, Cooke, & Johnson, 2013; Kivimäki et al., 2017). During a follow-up between 1995 and 2014, Kivimäki et al., (2017) identified 1,600 cases of multi-morbidities in participants who did not have diabetes, CVD, or stroke at baseline. Also, when compared to individuals with a healthy weight, the risk of developing cardio-metabolic multi-morbidity in overweight individuals was twice as high, for those with class I obesity, the risk was almost five times higher, and for individuals with class II or III obesity, the risk was almost 15 times higher (Kivimäki et al., 2017). Although the relationship between overweight & obesity and individual cardio-metabolic diseases has been well established, an understanding of the association of overweight & obesity and cardio-metabolic multi-morbidities is continuing to be developed.

Multi-morbidities are of serious concern due to their potential impact on health, and their prevalence. There is a prevalence of multi-health disorders in the U.S. In 2010, 31.5% of adults had multiple chronic conditions (Gerteis et al., 2014), and the prevalence increased to 42% in 2014 (Buttorff, Ruder, & Bauman, 2017). Also, women ages 18 to 64 years have a higher prevalence of multiple chronic conditions than men (Buttorff et al., 2017). The two conditions that are most prevalent in U.S. adults are hypertension and hyperlipidemia (Buttorff et al., 2017; Gerteis et al., 2014), which are both associated with overweight and obesity. Hypertension and hyperlipidemia, precede and lead to heart disease and stroke; and several of the underlying pro-inflammatory mechanisms of hypertension are similar pro-inflammatory mechanisms of hyperlipidemia (Alpert, Karthikeyan, Abdullah, & Ghadban, 2018). In addition, T2D increases the risk of heart disease and stroke because high blood glucose, over time, causes denervation of the nerves that control the heart and blood vessels, and it causes endothelial cell dysfunction and glycosylation of extracellular matrix proteins. T2D can also lead to the development of atherosclerosis (Kolluru, Bir, & Kevil, 2012), and T2D is linked to cancer (Joshi, Liu, & Turner, 2015). Currently, the mechanisms that are responsible for linking T2D to cancer are not definitively evident, but it has been proposed that the underlying inflammatory mechanisms by which diabetes affects cancer are the same inflammatory mechanisms that underlie obesity's contribution to cancer (Crujeiras, Díaz-Lagares, Carreira, Amil, & Casanueva, 2013; Joshi et al., 2015). In addition, although the relationship between T2D and cancer are not completely clear, it appears the changes in hormone and nutrient levels, as well as activation of inflammatory and stress-related pathways are contributing factors (Crujeiras et al., 2013; Joshi et al., 2015; Tilg & Moschen, 2014). It is clear that overweight conditions and obesity are chronic conditions that induce hypertension, heart disease, stroke, T2D, and cancer.

## Hypertension

Hypertension is associated with obesity, but ≥70% of cases of hypertension are related to obesity (Faulkner & Belin de Chantemèle, 2018). Hypertension is characterized by having a systolic blood pressure of ≥140 mmHg or a diastolic blood pressure of ≥90 mmHg. While the mechanisms that link overweight and obesity to hypertension are not definitive, excess adiposity has been identified as a factor that alters sympathovagal balance by increasing sympathetic activity of the heart. Increased sympathetic activity increases vasoconstriction and results in elevated blood pressure, and increased blood pressure fosters stiffening of the arteries, which can further contribute to underlying hypertension mechanisms (Arakeri, & Patil, 2018). In addition, obesity and arterial stiffening increase with age (Briant, Charkoudian, & Hart, 2016).

### Women and Hypertension

Women are particularly at risk for hypertension. Women have presented a higher prevalence of hypertension than men (Xiao, Wang, Sa, Qiu, Liu, 2019). Loss of estrogen in menopausal women is mechanistically linked to a decrease in β-adrenergic vasodilatation, which increases risk of hypertension in older women (Briant, et al., 2016). Estrogen regulates nitric oxide, and nitric oxide is responsible for vasodilation (Papakonstantinou et al., 2013). However, due to the significant decline of estrogen in menopausal women, vasodilation that results from estrogen-fostered mechanics decreases, thereby resulting in abnormal constriction of the blood vessels and causing hypertension.

Interestingly, for obese women who are not menopausal, estrogen does not appear to especially protective against hypertension. However, BMI has been reported as a contributing factor in this population (Faulkner & Belin de Chantemèle, 2018). There is more of a relationship

between increased BMI and blood pressure in women than in men, and the increased blood pressure has demonstrated no association with menopause (Faulkner & Belin de Chantemèle, 2018). Also, T2D in obese women removes protective hormonal effects of hypertension and coronary heart disease (Faulkner & Belin de Chantemèle, 2018).

**Leptin and Hypertension**

For women who are not menopausal, in addition to BMI, it appears that the link between obesity and hypertension is governed by the adverse effects of leptin. Leptin is an adipokine hormone that is produced by fat cells. It is responsible for appetite regulation and fat storage, and in obese individuals, it plays a significant role in blood pressure regulation (Faulkner & Belin de Chantemèle, 2018). Women, in general, have higher levels of leptin and a greater expression of leptin receptors compared to men because female adipocytes release more leptin per gram of fat mass than male adipocytes (Faulkner & Belin de Chantemèle, 2018). Faulkner and Belin de Chantemèle (2018) infer that leptin mediates hypertension in obese women through activation of the aldosterone mineralcorticoid receptor axis. Increased levels of aldosterone correlate with adipose tissue and BMI. This correlation has been more evident in women than men (Faulkner & Belin de Chantemèle, 2018). Also, leptin's activity in relation to aldosterone may explain why the protective effects of estrogen against hypertension in premenopausal obese women are diminished.

**Effects of Exercise on Hypertension**

Although leptin is an underlying mechanism of hypertension in obese women, four-weeks and eight-weeks of exercise training have demonstrated significant positive effects on leptin (Jackson et al., 2018). And in a meta-analysis, exercise demonstrated a significant reduction

of leptin in overweight and obese populations (Lin, Hu, Yan & Zhang, 2017). Therefore, exercise can reduce leptin, which can ultimately reduce hypertension.

Also, it is widely accepted that aerobic training could prevent or moderate hypertension in menopausal and post-menopausal women (Cardoso et al., 2011). In post-menopausal women, estrogen therapy is generally used to combat chronic symptoms and health disorders of menopause, but regarding hypertension, estrogen therapy has been shown to both increase, decrease, and have no effect on blood pressure (Cardoso et al., 2011). While the variability in blood pressure is not completely clear, Cardoso et al. (2011) have demonstrated that aerobic training moderates increased blood pressure in this population. One obvious reason why aerobic exercise is recommended for menopausal and post-menopausal women is because of its ability to reduce arterial stiffness (Li et al., 2015; O'Donovan et al., 2014). Menopause, age and adiposity are associated with arterial stiffness (Fernandes et al., 2018; O'Donovan et al., 2014). Therefore, menopausal and post-menopausal women who are overweight and obese would especially benefit from aerobic activity due to its ability to reduce arterial stiffness, and ultimately blood pressure in individuals who are hypertensive.

## Heart Disease

Hypertension can lead to heart disease and stroke and being overweight or obese increases the risk of developing heart disease and stroke (Faulkner & Belin de Chantemèle, 2018). As discussed previously, increased sympathetic activity, loss of estrogen, and increased levels of leptin are neuro-hormonal mechanisms that link obesity to hypertension-related heart disease.

### Changes in Cardiac Morphology, Hemodynamics, and Function

For hypertensive obese individuals, left ventricular (LV) pre-load and afterload increase, which can lead to changes in cardiac morphology and function (Alpert et al., 2018). Changes in

cardiac morphology can eventually lead to LV hypertrophy, LV diastolic dysfunction, and ultimately heart failure (Alpert et al., 2018). LV hypertrophy occurs as a result of increased LV load. Increased load puts more stress on the LV, and the ventricle thickens in order to normalize wall stress. The wall thickening eventually decreases LV compliance and LV diastolic filling (Shapiro & Ibrahim, 2017). Decreased LV compliance and LV diastolic filling causes preserved ejection fraction, which are characteristics of diastolic heart failure. As a result, because the LV is unable to sufficiently pump blood out of the heart, the volume of blood increases in the left atrium, causing atrial enlargement, and then blood eventually backs up, causing congestion of fluid in the lungs. Eventually, the congestion of fluid (congestive heart failure) leads to death if it is not recognized early and treated (Shapiro & Ibrahim, 2017).

Hemodynamic alterations also occur as a result of being obese and cause changes in cardiac morphology function. An increase in central and total blood volume has been associated with excess adiposity, which contributes to an increase in cardiac output. For the heart to increase cardiac output, the LV wall thickens in order to compensate for the LV load (as described above). This mechanism of cardiac compliance can also eventually lead to congestive heart failure (Alpert et al., 2018; Shapiro & Ibrahim, 2017). Changes in hemodynamics and morphology worsen with the severity of obesity (Alpert et al., 2018).

**Neuro-Hormonal and Metabolic Alterations**

Neuro-hormonal and metabolic alterations occur from altered mechanisms of angiotensin II (AG II) and leptin, and insulin resistance and hyperinsulinemia (Alpert et al., 2018). Each of these mechanisms contribute to hypertension. As described previously, hypertension is a contributing factor of changes in cardiac morphology and function.

Adipocytes increase production of AG II, which is a hormone that is part of the renin-angiotensin system (Alpert et al., 2018). AG II causes vasoconstriction and the release of aldosterone, which promotes retention of sodium by the kidneys. AG II's effects on vasoconstriction contribute to the development of hypertension, which causes an increase in LV afterload; and AG II's effect on aldosterone contributes to an increased blood volume, and ultimately increases LV pre-load. These functional changes of the LV can eventually lead to heart failure. Adipocytes also increase leptin levels, and increased adipocytes contribute to insulin resistance and hyperinsulinemia. Sympathetic nervous system (SNS) activity has also been found to be stimulated by these factors (Alpert et al., 2018), and stimulation of the SNS facilitates increased heart rate, decreased heart rate variability, and increased contractility of the myocardium; which are indicative of enhanced cardiac output and LV stroke volume (Alpert et al., 2018).

**Leptin and Heart Disease**

As discussed previously, leptin is an adipokine hormone that plays a significant role in blood pressure regulation. Obesity elevates serum leptin levels due to leptin resistance, which results in hyperleptinemia. Hyperleptinemia has led to cardiac remodeling through mechanisms that facilitate hypertrophy, reduced myocardial contractility, diastolic dysfunction, and inflammation of the myocardium (Alpert et al., 2018); and it contributes to atherogenesis (Koh, Park, & Quon, 2008). Hyperleptinemia increases SNS activity, which promotes LV hypertrophy by increasing LV afterload (Alpert et al., 2018; Karmazyn, Gan, & Rajapurohitam, 2013). Hyperleptinemia also promotes oxidation of fatty acids in cardiomyocytes, which leads to increased triglycerides stores (Alpert et al., 2018; Ellulu, Patimah, Khaza'ai, Rahmat, & Abed, 2017). Oxidation of fatty acids in cardiomyocytes can lead to interstitial toxicity of ceramides in the myocardium,

and this can attenuate myocardial contractility (Alpert et al., 2018). Hyperleptinemia also increases activity of metalloproteinases and other enzymes in the extracellular matrix of the myocardium, which promotes interstitial fibrosis and diastolic dysfunction (Alpert et al., 2018; Ellulu et al., 2017).

Hyperleptinemia also has a role in promoting atherogenesis. Atherogenesis occurs as a result of its increased activity as a pro-inflammatory cytokine and oxidative stress. Increased activity of pro-inflammatory cytokines and oxidative stress contribute to nitric oxide bioavailability, which is a central part of endothelial dysfunction of the arteries (Koh et al., 2008; Wende, Symons, & Abel, 2012). Dysfunction of arterial endothelium leads to inflammation of the arterial wall. Inflammation of the arterial wall and lipid accumulation, particularly LDLs, develops into what is known as atherosclerosis (Wende et al, 2012). Therefore, leptin is a central pro-inflammatory marker of heart disease. Increased levels of leptin contribute to overall myocardial dysfunction and arterial damage (Alpert et al., 2018; Koh et al., 2008; Wende et al, 2012).

**Adiponectin and Heart Disease**

Adiponectin is another adipokine that is produced by adipocytes, and it is responsible for regulating lipid and energy metabolism (Ellulu et al., 2017). It is an anti-inflammatory cytokine that improves endothelial function, inhibits atherosclerosis, and reduces insulin resistance. It also inhibits apoptosis of ischemia-reperfusion injury in the myocardium, and it inhibits cardiac hypertrophy and myocardial fibrosis (Alpert et al., 2018; Hui, Lam, Vanhoutte, & Xu, 2012). However, adiponectin is down-regulated in obesity, which is due to chronic inflammation of adipose tissue, mediated by increased levels of pro-inflammatory markers such as IL-6, C-reactive protein (CRP) (Abraham et al., 2017; Ellulu et al., 2017), and TNF-α (Orrù et al., 2017). Due to

down-regulation of adiponectin in obesity, its cardio-protective benefits are reduced. Low adiponectin, in animal models, has demonstrated an association with atherogenesis, endothelial dysfunction, apoptosis after ischemia-reperfusion injury, and increased renin-angiotensin aldosterone, sympathetic nervous system activation, hyperleptinemia, and insulin resistance (Alpert et al., 2018; Hui et al., 2012). However, these findings imply that the same mechanisms occur in humans and appear to be supported by investigations that have demonstrated that adiponectin administration has insulin-sensitizing, anti-atherogenic, and anti-inflammatory effects (Achari & Jain, 2017). In summary, low levels of adiponectin that are associated with obesity appears to promote development of LV hypertrophy, LV diastolic dysfunction, and LV systolic dysfunction (Alpert et al., 2018).

**Insulin Resistance, Hyperinsulinemia, and Heart Disease**

Insulin is an anabolic hormone secreted from pancreatic β-cells that stimulates the synthesis and storage of carbohydrates, lipids, and proteins. Insulin resistance is an impaired response to insulin stimulation of the target tissues, primarily liver, muscle, and adipose tissue (Page & Johnson, 2018). Hyperinsulinemia is an excess level of circulating insulin when compared to the level of circulating glucose.

Insulin resistance leads to hyperinsulinemia, and they are associated with obesity (Page & Johnson, 2018). Insulin resistance also contributes to altered cardiac structure and function. It is associated with increased LV mass and decreased myocardial performance (Alpert et al., 2018). Also, insulin resistance has been associated with increased fatty acid uptake, utilization, and oxidation in cardiomyocytes (Alpert et al., 2018) leading to cardiac lipotoxicity, which is an excessive accumulation of fatty acids and triglycerides in the myocytes. Triglyceride accumulation in the myocytes has been correlated with mitochondrial dysfunction that leads to apoptosis (Wende

et al, 2012); and cardiac lipotoxicity has been shown to lead to myocardial lipid accumulation due to an inhibition of triglyceride lipase (Alpert et al., 2018). These mechanisms of cardiac lipotoxicity promote cardiomyocyte death, LV systolic and diastolic dysfunction and the development of myocardial fibrosis (Alpert et al., 2018; Wende et al, 2012).

In addition to altered cardiac structure and function, insulin resistance is a risk factor for atherosclerosis. Insulin has mitogenic pathways that can promote altered cell growth of monocytes, and this mechanism can alter the endothelium of the arteries. As a result, damage to the arterial wall occurs, and this damage contributes to the progression of atherosclerotic plaque (Razani, Chakravarthy, & Semenkovich, 2008; Wende et al, 2012). In addition to insulin's ability to alter cell growth of monocytes in the endothelium, insulin is also associated with altering nitric oxide activity of the endothelium (Wende et al, 2012). Insulin resistance appears to make the endothelium less responsive to nitric oxide vasodilation (Razani et al., 2008; Wende et al, 2012). When vessels are less responsive to vasodilation, chronic constriction of vasculature can cause chronic hypertension, which can eventually lead to LV hypertrophy and ultimately heart failure.

The metabolic effects of insulin resistance and hyperinsulinemia on cardiac structure, function, and vessels can be detrimental to cardiovascular health; and being overweight or obese is associated with insulin resistance and hyperinsulinemia. Therefore, being overweight or obese increases the risk of developing heart disease not only by inflammatory mechanisms that stem from, for example, increased levels of leptin, but also by mechanisms that develop from metabolic dysregulation of insulin.

**Abdominal Obesity and Heart Disease**

Abdominal obesity is the presence of excessive fat around the abdomen that can negatively affect health (Chrostowska, Szyndler, Paczwa, & Narkiewicz, 2011). Abdominal obesity is

indicative of having higher visceral adipose tissue. Visceral adipose tissue is fat that surrounds the organs, and an increased amount of this tissue increases free fatty acid (FFA) secretion and pro-inflammatory cytokines such as C-reactive protein, TNF-α, and IL-6. These mechanisms are known to contribute to CVD and its risk factors: dyslipidemia, hypertension, and T2D (Sanguankeo et al., 2017). Waist measurements of ≥40 inches for men, and ≥35 inches for non-pregnant women are indicative of being at higher risk for developing CVD (Turner et al., 2012). Chrostowska et al. (2011) found that increasing waist circumference is significantly associated with hypertension and CVD. Also, the INTERHEART study, a case-control study that assessed obesity and the risk of myocardial infarction in 27, 098 participants, found that abdominal obesity was the strongest risk factor for myocardial infarction, followed by BMI (Chrostowska et al., 2011). Changes in cardiac morphology has also been associated with abdominal obesity. Vernooij et al. (2012) found a positive relationship between waist circumference and magnetic resonance imaging (MRI)-LV mass; and Maltsev, Shiskin, and Pchelin (2014) reported that waist circumference is associated with echocardiography-LV mass. Abdominal adiposity is also independently associated with subclinical LV systolic dysfunction (Russo et al., 2016), and cardiac structural remodeling, fibrosis, and diastolic dysfunction have been detected in healthy subjects with abdominal obesity (Eschalier et al., 2014).

Being overweight or obese increases the risk of heart disease. However, in addition to having general excess adiposity, excess adiposity around the waist present increased risk of developing CVD (Sanguankeo et al., 2017). Changes in cardiac morphology and function can occur from both general adiposity and abdominal adiposity, and these changes can ultimately lead to heart failure. Therefore, overweight and obesity pose a serious risk to cardiovascular health.

## Heart Disease and Women

The underlying mechanisms of CVD due to overweight and obesity affect both men and women, and men have a higher rate of mortality from CVD than women (Xu, Murphy, Kochanek, & Bastian, 2013). However, women have higher perioperative mortality and higher periprocedural complication rates than men (Papakonstantinou et al., 2013). These incidences may be attributed to women having smaller and stiffer hearts, and smaller and stiffer vasculature (Papakonstantinou et al., 2013). Also, the female vasculature presents considerably greater atherosclerosis and endothelial and smooth muscle dysfunction; and in exercise stress tests, women more often present with angina due to endothelial dysfunction (Papakonstantinou et al., 2013). Women also have higher fat mass than men, and visceral adipose tissue in women is more strongly associated with cardiometabolic risk factors than visceral adipose tissue in men (Elffers et al., 2017; Schorr et al., 2018). Lew et al., (2017) found that obese women have significantly higher levels of leptin and C-reactive protein than obese men. C-reactive protein is an inflammatory marker that is associated with inflammation of the arteries. Although men have a higher rate of mortality from CVD than women, the risk and detriment of heart disease in overweight and obese women is of special concern due to differences in heart and vasculature size, fat mass and body fat distribution, and neuro-hormonal and inflammatory markers.

## Effects of Exercise on Inflammatory Cytokines and Visceral Fat

Inflammatory cytokines and visceral adipose tissue link overweight and obesity to CVD. However, regular exercise has a positive effect on inflammatory cytokines and visceral adiposity. A lack of regular exercise or inactivity is related to CVD, and in an animal model, cessation of exercise led to significant increases in intra-abdominal fat within 21 days (Slentz, Houmard, & Kraus, 2009). In a randomized controlled trial, six months of inactivity from the control group

(sedentary individuals) demonstrated increased body weight, total abdominal fat, waist circumference, waist-to-hip ration, and visceral fat (Slentz et al., 2009). However, data from Wedell-Neergaard et al. (2018) suggests that cardio-respiratory fitness reduces abdominal obesity. Also, a 12-week exercise program and a 12-month exercise program have both demonstrated a significant decrease in visceral adipose tissue, as measured by computer tomography scan (Slentz et al., 2009).

In addition to reducing abdominal obesity and visceral adipose tissue, regular exercise has demonstrated anti-inflammatory effects. Exercise has been shown to reduce pro-inflammatory cytokines and increase anti-inflammatory cytokines. Verheggan et al. (2018) found that walking attenuated pro-inflammatory cytokines in both lean and overweight-obese individuals, and cardiorespiratory fitness has been inversely associated with high sensitive C-reactive protein, IL-6, and IL-18; and directly associated with the anti-inflammatory cytokine IL-10 (Wedell-Neergaard et al., 2018; Zoeller, 2008). In addition to reducing interleukin cytokines, physical activity also decreases TNF-α and interferon-y (IFN-y) (Palmefors, DuttaRoy, Rundqvist, & Börjesson, 2014). TNF-α and IFN-y promote atherosclerosis (Kleinbongard, Heusch, & Schulz, 2010; McLaren & Ramji, 2009), which can lead to ischemia-reperfusion and ultimately result in heart failure. However, exercise has demonstrated non-pharmacological effects by reducing the risk of CVD through reducing inflammatory cytokines and visceral adipose tissue.

## Stroke

Stroke is either caused by embolism or atherosclerosis, which blocks blood flow to the brain and causes tissue death; or it is caused by aneurysm, which leads to cerebral malfunction due to bleeding on the brain. Adiposity is significantly associated with increased risk of stroke. For every single unit increase in BMI, the risk of ischemic stroke increases 5%, starting with a

normal BMI of 20 kg/m$^2$ (Kernan et al., 2013). Hypercholesterolemia, hypertension, insulin resistance, and pro-inflammatory cytokines markedly explains obesity's association with increased risk of stroke. These pathologies can result in progressive atherosclerosis or thromboembolism, which can lead to cerebrovascular arterial occlusion or rupture (Kernan et al., 2013). Obesity is also attributed to stroke-associated atrial fibrillation and obstructive sleep apnea (Kernan et al., 2013).

**Insulin Resistance and Stroke**

Obesity leads to arterial and metabolic disorders that affect the entire cardiovascular system. As discussed earlier, insulin resistance is a metabolic disorder that may lead to atherosclerosis (Razani et al., 2008; Wende et al, 2012). Atherosclerosis affects both the heart and the brain. Atherosclerosis is an accumulation of plaque from lipids, and this build-up of plaque in the cerebral vasculature can cause either atherothrombotic stroke or cerebral embolism. Atherothrombotic stroke is the most common cause of stroke, and it results from the formation of a blood clot on atherosclerotic plaque within a blood vessel in the brain. A clot can reduce and fully block blood flow to the part of the brain where it is located. Cerebral embolism occurs when an embolus lodges in an artery leading to or in the brain, and the embolus blocks the flow of blood. The embolism can occur due to broken atherosclerotic plaque (Powers et al., 2018). In addition to atherosclerosis, thromboembolism can occur as a result of hypercoagulability and enhanced platelet aggregation. This mechanism of thromboembolism is associated with insulin resistance (Kernan et al., 2013). Insulin resistance, as discussed earlier, is not only associated with atherosclerosis of cardiovascular and cerebrovascular vessels, but it is also associated with thromboembolism. Therefore, the metabolic dysfunction of insulin increases the risk of stroke, particularly in overweight and obese individuals.

## Pro-Inflammatory Signaling and Stroke

Pro-inflammatory signaling from cytokines, such as TNFα and IL-6, leads to upregulation of C-reactive protein (Kernan et al., 2013), which contributes to vascular inflammation. Vascular inflammation leads to vascular vulnerability, which promotes atherosclerosis and atherothrombosis. Increased local expression of adhesion molecules and decreased endothelial bioactivity of nitric oxide occurs from the underlying pro-inflammatory mechanisms (Cozlea et al., 2013; Kernan et al., 2013). In addition to vascular inflammation that occurs as a result of underlying pro-inflammatory signaling from cytokines, AG II plays a role in inflammatory mechanisms. In recent years, research has documented activity of AG II as a pro-inflammatory molecule (Benigni, Cassis, & Remuzzihas, 2010). Production of AG II from adipocytes, an underlying mechanism of hypertension, leads to narrowing and rupture of blood vessels (aneurysm), and it can lead to the development of an embolism (Kernan et al., 2013). Inflammatory mechanisms that are related to overweight and obesity can result in damage to cerebral vessels, and this damage can lead to atherosclerosis and atherothrombosis that can cause stroke.

## Atrial Fibrillation, Obstructive Sleep Apnea, and Stroke

In addition to insulin resistance and pro-inflammatory signaling, atrial fibrillation (AF) can also induce stroke in overweight and obese individuals. AF positively correlates with BMI, and being overweight or obese contributes to higher incidence, prevalence, severity, and progression of AF (Nalliah, Sanders, Kottkamp, & Kalman, 2016). Also, AF risk is commonly attributed to other cardiovascular risk factors, which are T2D and hypertension (Nalliah et al., 2016). AF is a rapid heart rate that occurs when the atria beat out of rhythm with the ventricles. This irregular rapid heart rate does not allow blood to efficiently eject from the heart, which can cause blood to

pool and form an embolism (Kernan et al., 2013). The embolism can travel to the brain and block cerebral blood flow, causing oxygen deprivation (hypoxia) to the brain's tissue.

Another condition that can lead to hypoxia and result in stroke in overweight and obese individuals is obstructive sleep apnea (OSA). OSA has an indirect association with stroke that is linked to dysautonomia, hypertension, cardiac arrhythmia and impaired glucose tolerance (Sharma & Culebras, 2016). OSA is characterized by repetitive upper airway closures during sleep. The repetitive closure leads to oxygen desaturation and sleep fragmentation (Tasali, Van Cauter, Hoffman, & Ehrmann, 2008).

**Dysautonomia, hypertension, cardiac arrhythmia, and impaired glucose tolerance.**

Dysautonomia is a disorder of autonomic nervous system (ANS), and sleep apnea dysregulates the ANS. The suprachiasmatic nucleus (SCN), the body's biological clock, generates autonomous rhythmic activity. The SCN plays a role in sympathetic–parasympathetic balance, hepatic glucose production and insulin sensitivity (Sharma & Culebras, 2016). When OSA occurs, it causes a decrease in ion arterial oxygen tension and an increase in arterial carbon dioxide tension. These arterial mechanisms generate an increase in sympathetic nervous system activity, which causes peripheral vasoconstriction and increases both nocturnal and daytime blood pressure, causing hypertension (Sharma & Culebras, 2016). OSA's association with atrial fibrillation is explained by an increase in negative intrathoracic pressure during episodes of apnea. The increase in negative intrathoracic pressure causes an increase in cardiac vagal output, which induces atrial fibrillation (Sharma & Culebras, 2016).

OSA's association with impaired glucose tolerance and insulin resistance have been explained by impaired hepatic glucose production and insulin sensitivity, however the underlying mechanisms are not fully understood (Kernan et al., 2013; Sharma & Culebras, 2016; Tasali et

al., 2008). Previous research has demonstrated improved insulin sensitivity and glucose tolerance with successful OSA medical therapy, such as the use of a continuous positive airway pressure (CPAP) machine (Kernan et al., 2013; Tasali et al., 2008).

### Treatment, Exercise, and Stroke in Women

In addition to medical therapy, weight-loss demonstrates significant improvement of OSA (Kuna et al., 2013; Tuomilehto, Seppä, & Uusitupa, 2013). Excess weight is the most common cause of OSA, and weight-loss is generally recommended for successful treatment.

Also, as discussed earlier, regular exercise and aerobic training aid in averting vascular disorders of the heart and brain (Verheggan et al., 2018; Wedell-Neergaard et al., 2018). For women, promotion of regular exercise is especially important because one in five women in the U.S. will have a stroke, almost 60% of stroke-deaths are in women, and stroke kills twice as many women as breast cancer (Benjamin et al., 2019). Interventions have demonstrated improved knowledge about stroke and health behaviors among female subjects, and moderate to vigorous-intensity physical activity has been associated with a lower risk of ischemic stroke (An et al., 2018; Willey et al., 2019). Therefore, physical activity interventions can aid in reducing stroke-deaths in women.

## Type 2 Diabetes (T2D)

T2D is associated with overweight and obesity. The link between obesity and T2D is well established, and obesity is believed to account for 80-85% of the risk of T2Ds development (Eckel, et al., 2011). Excess adiposity hinders insulin responsive cells from properly using insulin to transport glucose into the cell for glucose to be metabolized (Eckel, et al., 2011). This leads to hyperglycemia (increased serum glucose). Increased serum glucose through glycated hemoglobin (A1C) testing is used to diagnosis this disease and having an A1C of 6.5% or higher on

two separate occasions indicates the diagnosis of diabetes (American Diabetes Association, 2016).

T2D can be detrimental to the neurological and cardiovascular systems. It can lead to retinopathy, nephropathy, neuropathy, and microvascular and macrovascular disease, which increases the risk of stroke and heart failure (Chawla, Chawla & Jaggi, 2016). Hyperglycemia, over time, can cause nerve damage. Also, insulin resistance leads to hyperinsulinemia, which is associated with increased oxidative stress, protein kinase activation, and advanced glycation end products, which are mechanisms that damage the vascular endothelium (Chawla et al., 2016).

**Mitochondrial DNA Damage**

Abnormal circulating levels of blood glucose and insulin, and oxidative stress and inflammation are associated with mitochondrial DNA damage (Włodarczyk & Nowicka, 2019). Enhanced ROS production alter DNA damage response by the inhibition of DNA repair enzymes, a mechanism that may lead to DNA lesions. DNA lesions are DNA damage that can result from the absence of nucleotide excision repair mechanisms in the mitochondria (Włodarczyk & Nowicka, 2019). The mitochondria are large organelles that are found in most bodily cells, and they are primarily responsible for cellular respiration and energy production. Damage to mitochondrial DNA leads to enhanced mitochondrial DNA degradation and decreased DNA copy for production of new mitochondrial organelles; resulting in systemic mitochondrial dysfunction. Mitochondrial dysfunction leads to poor fatty acid (FA) oxidation and disturbances in glucose homeostasis (Włodarczyk & Nowicka, 2019). Mitochondrial dysfunction ultimately leads to impairment of insulin sensitivity (Wang, Wang, Huang, & Wei, 2013; Włodarczyk & Nowicka,

2019). Also, oxidized mitochondrial DNA has demonstrated an induced synthesis of pro-inflammatory cytokines by activation of toll-like receptor 9 (Heinonen et al., 2015; Włodarczyk & Nowicka, 2019).

**Pro-Inflammatory Cytokines and Insulin Resistance**

The increase of pro-inflammatory cytokines occurs due to mitochondrial DNA damage and adipocyte membrane rupture due to hypertrophy (Quail & Dannenberg, 2019; Włodarczyk & Nowicka, 2019). An overabundance of pro-inflammatory cytokines interferes with insulin signaling in insulin target tissues: adipose tissue, liver, and skeletal muscle (Mauer, Denson, & Brüning, 2015). Insulin signaling regulates glucose, lipid, and energy homeostasis, primarily by the liver, skeletal muscle, and adipose tissue. Altered insulin signaling in both subcutaneous and visceral adipose tissue are associated with insulin resistance, however research suggests that visceral adiposity is more of a contributing factor (Hocking, Samocha-Bonet, Milner, Greenfield, Chisholm, 2013); Patel & Abate, 2013).

Chronic exposure to pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β in adipose tissue, the liver, and skeletal muscle leads to dysregulation of insulin signaling, which can ultimately result in insulin resistance (Benito, 2011). Insulin resistance alters lipid metabolism in adipose tissue and glucose homeostasis in skeletal muscles (Benito, 2011). The liver also plays a major role in maintaining normal blood glucose levels by regulating glucose production (gluconeogenesis), and the breaking-down of glycogen (glycogenolysis). In the liver, expression of glucose-6 phosphatase (a gluconeogenic enzyme) becomes altered by chronic levels of IL-6, which leads to increased hepatic glucose production (Mauer, Denson, & Brüning, 2015). Dysregulation of glucose homeostasis in the liver, and in adipose and skeletal muscle tissues due to insulin resistance leads to an abnormal sustained increase in blood glucose. The sustained increase in

blood glucose caused by insulin resistance is defined as T2D, and the underlying mechanisms of excess adiposity explain its association with overweight and obesity.

**Leptin and Insulin**

Leptin is a hormone that is primarily responsible for regulating energy. It is also a pro-inflammatory agent that is released from adipose tissue, and dysregulation of leptin affects energy expenditure, lipid, and glucose metabolism. Leptin has been found to mediate insulin secretion and sensitivity in peripheral tissues, and leptin has demonstrated a significant positive correlation with insulin in patients with new diagnoses of T2D (Moonishaa et al., 2017). However, because both leptin and insulin share a common role in energy metabolism and glucose homeostasis, research has demonstrated contraindicative findings of leptin's association with insulin. Previous and current research has demonstrated a relationship between leptin and insulin that suggests leptin plays a role in insulin resistance, metabolic syndrome, and T2D (Ghadge & Khaire, 2019; López-Jaramillo et l., 2014). However, research has emerged that suggests that leptin can positively contribute to insulin sensitivity and glucose homeostasis, which translates into leptin possibly being an anti-diabetic agent (Paz-Filho, Mastronardi, Wong, & Licinio, 2012). This may be due to leptin and insulin having the ability to regulate one another (Amitani, Asakawa, Amitani, & Inui, 2013).

Leptin has been shown to inhibit insulin, but insulin has also been shown to stimulate leptin synthesis and secretion (Amitani et al., 2013; Paz-Filho et al., 2012). Also, leptin has been shown to decrease hepatic production of glucose from the liver, which contributes to its glucose-lowering effects (Amitani et al., 2013; Paz-Filho et al., 2012). Researchers are now suggesting that leptin can potentially be used as a therapy for treating both T1D and T2D (Amitani et al.,

2013; Paz-Filho et al., 2012). Therefore, although a body of research supports a positive correlation between leptin and insulin in overweight and obese individuals and in patients with T2D (Ghadge & Khaire, 2019; López-Jaramillo et a l., 2014; Moonishaa et al., 2017), and a positive correlation between hyperleptinemia and hyperinsulinemia (Chen, Balland, & Cowley, 2017); it is possible that increased levels of leptin or hyperleptinemia may not contribute to facilitating insulin resistance, or leptin may not be a contributing agent in the development of T2D. However, additional experiments and clinical trials are needed in order to validate the suggestive findings of leptin being a potential anti-diabetic agent.

**Diabetic Dyslipidemia**

There is a link between insulin resistance and diabetic dyslipidemia. Lipid abnormalities in T2D is common and is characterized by lowered HDLs and elevated triglycerides (Mahishale, Allolli, Bidri, & Balaganur, 2018). This disorder is known as diabetic dyslipidemia. Activity of intracellular hormone-sensitive lipase can be triggered by insulin resistance. Intracellular hormone-sensitive lipase increases the release of non-esterified fatty acids (NEFA) from triglycerides stored in adipose tissue, and high circulating levels of NEFA increases the production of hepatic triglycerides (Ormazabal et al., 2018; Schofield, Liu, Rao-Balakrishna, Malik, & Soran, 2016). Increased hepatic triglycerides is associated with increased secretion of apolipoprotein B (apoB). This is linked to insulin reducing the normal inhibitory effect of hepatic apoB production and triglyceride secretion in very-low density lipoproteins (VLDL). As a result, the secretion of VLDL becomes larger and more abundant in triglycerides (Schofield et al., 2016). This underlying mechanism results in hypertriglyceridemia (Ormazabal et al., 2018; Schofield et al., 2016). In addition, triglyceride-rich lipoproteins (e.g., VLDL) are a primary mechanism by which LDLs are generated, and HDLs are reduced in diabetes (Schofield et al., 2016).

Increased triglycerides and LDLs, and reduced HDLs are physiological factors that put T2D individuals at risk for developing coronary heart disease and atherosclerosis (Mahishale et al., 2018; Ormazabal et al., 2018; Schofield et al., 2016). However, these conditions can even develop before a diagnosis of T2D. Increased cardiovascular risk commonly exists before the onset of hyperglycemia. Obesity and insulin resistance, which are signs of metabolic syndrome, are often present for several years prior to T2D diagnosis, and they are associated with hypertension and dyslipidemia. Adults with diabetes are two to four times more likely to die from heart disease than individuals without diabetes. Also, 68% of individuals who are 65 years and older with diabetes die from heart disease, and 16% die from stroke (Powers et al., 2018). Being overweight or obese carries serious health risks in relation to the metabolic disorders that are associated with the onset of T2D and its connection to heart disease. Although T2D is not a direct cause of heart disease, their pathologies are interconnected, and one does not appear to become present without the other.

**T2D and Women**

Diabetes affects women differently than men. Women with diabetes are at higher risk for heart disease, have lower survival rates and poorer quality of life after a diabetes-associated heart attack, are at higher risk for blindness, and are at higher risk for depression (Pan et al., 2010). Also, women who are overweight or obese are at higher risk for developing gestational diabetes (Chu et al., 2007). Gestational diabetes increases the risk of developing T2D seven-fold, and over half of women with gestational diabetes develop T2D within 5 to 10 years postpartum (Herick et al., 2019; Nabuco et al., 2016). Menopause is another factor that negatively impacts T2D in women. Metabolic disorders, particularly impaired glucose tolerance, insulin resistance, hyperinsulinemia, and T2D are adverse effects of hypoestrogenism, and women are at increased

risk of developing T2D during the menopausal and post-menopausal life-stage (Stachowiak, Pertyński & Pertyńska-Marczewska, 2015).

### Exercise and T2D

Exercise is an important component for treating T2D. At least 30 minutes of moderate to vigorous aerobic exercise five days per week, or at least 150 minutes per week is recommended (American Diabetes Association, 2016). The greatest benefit of exercise for T2D management are the acute and chronic improvements of insulin activity. Most individuals experience a decrease in blood glucose during mild to moderate exercise, and between two and 72 hours afterward (Colberg et al., 2010). Exercise of any intensity stimulates blood glucose uptake for glycogen synthesis, and it stimulates fat oxidation. However, moderate to vigorous intensity exercise enhances glucose uptake and fat oxidation, which is centrally rendered by increased insulin activity (Burr, Rowan, Jamnik, & Riddell, 2010; Colberg et al., 2010). Moderate-intensity aerobic activity aids in reducing liver fat, which facilitates an increase in hepatic and peripheral insulin activity; and moderate-intensity aerobic activity enhances the responsiveness of skeletal muscles to insulin, with increased expression of enzymes that are involved in glucose metabolism and insulin signaling (Burr et al., 2010; Colberg et al., 2010). Exercise has significant beneficial effects on T2D, as it aids in controlling blood glucose by improving insulin activity and the expression of enzymes that are responsible for glucose metabolism.

## Cancer

Overweight and obesity are associated with at least 13 types of cancer, and they account for up to 40% of all diagnosed cases (Massetti, Dietz, & Richardson, 2017). The 13 cancers that are associated with overweight and obesity are: meningioma (cancer of the tissue covering the

brain and spinal cord), multiple myeloma (cancer of blood cells), adenocarcinoma of the esophagus, thyroid, liver, gallbladder, upper stomach, kidneys, pancreas, uterus, ovaries, colon & rectum, and breast cancer (Massetti et al., 2017). Overweight and obesity increase hormonal and inflammatory responses that lead to cancer (Crujeiras et al., 2013; Munir et al., 2018).

**Pro-inflammatory Cytokines and Cancer**

As discussed previously, TNF-α and IL-6 are cytokines that are over-abundantly expressed due to adipocyte hypertrophy and hyperplasia and are known for contributing to metabolic dysfunction. In addition to metabolic dysfunction, these cytokines and IFNγ and IL-1β have demonstrated upregulation of anti-apoptotic and angiogenic proteins in tumor cells (Crujeiras et al., 2013), and they play a pivotal role in tumorigenesis, tumor progression, and metastasis (Atretkhany, Drutskaya, Nedospasov, Grivennikov, & Kuprash, 2016; Zhang, Yang, Wang, & Zhang, 2018). The molecular and cellular mechanisms that exists between cancer stem cells and inflammatory cytokines explains how cancer is promoted by inflammation. Inflammatory cytokines enhance proliferation and survival signaling of cancer cells, and they induce metastasis (Atretkhany et al., 2016; Zhang et al., 2018).

**Leptin and Breast Cancer**

Leptin increases with adiposity, causing hyperleptinemia, which is known to lead to mitogenic, pro-inflammatory, anti-apoptotic, and proangiogenic activity in breast cancer cells (Danthala et al., 2018; De Pergola, & Silvestris, 2013). Obesity's association with leptin not only increases the risk of developing breast cancer, but it also increases the risk of reoccurrence and cancer death. Breast cancer has been the focus of most experimental studies that have investigated the effects of leptin, and results have demonstrated that leptin upregulates estrogen signaling, and it intensifies estrogen production (De Pergola, & Silvestris, 2013).

Estrogen is responsible for regulating energy metabolism, stress response, mineral balance, and sexual development. Estrogen is predominantly produced by the ovaries in premenopausal women, and very little to no estrogen is produced in post-menopausal women. Breast cancer diagnoses mostly occur when circulating levels of estrogen are low, which is after menopause (Bhardwaj et al., 2019). After menopause, the primary source of estrogen is adipose tissue, and BMI has been positively associated with tissue levels of estrogen (Bhardwaj et al., 2019). Aromatase, an enzyme that is responsible for catalyzing one of the final steps in estrogen biosynthesis, is expressed in breast adipose tissue, and it is hypothesized to be a major inducer of estrogen-dependent breast cancer after menopause (Bhardwaj et al., 2019). As fat mass increases, expression of aromatase increases and then estrogen levels rise. Leptin has demonstrated stimulation of aromatase expression (Bhardwaj et al., 2019). Therefore, it appears that leptin contributes to breast cancer by inducing expression of aromatase, and ultimately increasing breast estrogen levels, as adiposity increases.

**Adiponectin and Cancer**

Adiponectin is an anti-inflammatory cytokine that has anti-atherogenic and insulin-sensitizing properties. However, adiponectin also promotes cellular differentiation and apoptosis, and indirectly inhibits angiogenesis and cell migration. It also induces downregulation of vascular adhesion molecules, which reduces the spread of tumors. Adiponectin also prevents interaction of growth factors and their receptors (Danthala et al., 2018; De Pergola, & Silvestris, 2013), and it indirectly protects against carcinogenesis by decreasing the development of insulin resistance. However, due to adiponectin’s reduction from increased adipose mass, its anti-inflammatory properties are suppressed in obesity.

Adiponectin's circulating levels have been inversely related to cancer occurrence and cancer stage (De Pergola, & Silvestris, 2013). The inverse relationship between serum adiponectin levels and the risk of prostate, colorectal, breast, and endometrial cancer is evident and well-established (Izadi, Farabad, & Azadbakht, 2012; Katira & Tan, 2016). However, research suggests decreasing serum insulin levels are a possible mechanism for exerting adiponectin's protective effects against carcinogenesis, particularly for endometrial cancer (Izadi et al., 2012; Katira & Tan, 2016; Mihu, Ciortea, & Mihu, 2013). Adiponectin has an inverse relationship with estrogen, which suggests that adiponectin may play a role in controlling estrogen. Therefore, if the protective effects of adiponectin are exerted, estrogen does not abnormally increase, and the risk of carcinogenesis is reduced. Regarding the endometrium (inner lining of the uterus), it becomes abnormally thick when estrogen is present without enough progesterone, causing the cells of the endometrium to grow too quickly and ultimately form a tumor or tumors (Massetti et al., 2017). Research suggests if insulin is controlled, estrogen by this mechanism may not become a contributing factor of endometrial carcinogenesis.

**Insulin-Like Growth Factor-1 (IGF-1)**

In addition to hyperinsulinemia promoting carcinogenesis in the endometrium, and in the breast, colon, and prostate, IGF-1 increases the aggressiveness of these type of cancers (De Pergola, & Silvestris, 2013; Orrù et al., 2017). Insulin and IGF-1 interact with their receptors (insulin receptors and IGF-1 receptor). Interaction of IGF-1 with its receptors induces activation of kinases, which results in the loss of epithelial integrity and the promotion of cell migration, which can lead to tumor development (De Pergola, & Silvestris, 2013). Also, biochemical and functional analyses of tumors have demonstrated that when the interaction of both insulin-receptor and IGF-1-receptor are co-expressed in the same cell, a hybrid forms (insulin-receptor + IGF-

1-receptor) that mediates the effects of insulin and IGF-1, and ultimately stimulates cell proliferation (De Pergola, & Silvestris, 2013).

IGF-1 is a protein hormone that is mainly produced by the liver, it mediates anabolic functions, and it has demonstrated mitogenic and insulin-like metabolic activities (Orrù et al., 2017). Several hormones and growth factors influence its expression, and among them are estrogen and insulin (Orrù et al., 2017). High levels of serum insulin increases IGF-1 synthesis in the liver, which ultimately promotes IGF-1 bioactivity. IGF-1 impairs apoptosis, and induces metastatic tumor spread (De Pergola, & Silvestris, 2013), which has suggested its link to higher risk of breast, endometrial, colorectal, and prostate cancer (Danthala et al., 2018; Izadi et al., 2012; Orrù et al., 2017). Underlying mechanisms of increased IGF-1 bioactivity and hyperinsulinemia explain how being overweight and obese increase the risk of cancer development, reoccurrence, and death. Also, they provide insight as to how estrogen plays a role in the cancers that chronically impact women.

**Cancer in Women**

About two in three of all cancer diagnoses are in adults who are 50-74 years of age, and about 55% of all cancer diagnoses are in women (Massetti et al., 2017). In 2015, 282,107 women died of cancer in the U.S. and nine of the top ten cancers, by rate of deaths for women, are associated with obesity (breast cancer, colon and rectum, pancreatic, ovarian, uterine, leukemia, non-Hodgkin lymphoma, liver, and brain and other nervous system) (HHS, 2018b).

Cancer in women is of special concern because of its prevalence, and its association with obesity. Over the past 25 years, obesity has been attributed as a cause of more deaths from cancer in women than in men (De Pergola, & Silvestris, 2013). Excess adiposity increases circulating sex steroids, and BMI is a correlate of breast, endometrial, and other cancers linked to hormones

(De Pergola, & Silvestris, 2013; Mihu, 2013). Research has demonstrated that the risk of breast cancer in post-menopausal women increases due to higher levels of sex steroids, which include dehydroepiandrosterone (DHEA), DHEA sulfate, androstenedione, testosterone, estradiol, and low levels of sex hormone binding globulin (Bhardwaj et al., 2019; De Pergola, & Silvestris, 2013; Strong et al., 2015). Studies have also demonstrated that estrogen is mitogenic, it regulates the expression of insulin receptor substrate-1 in breast tissue, and it induces free radical-mediated DNA damage, genetic instability, and gene mutations (Bhardwaj et al., 2019; De Pergola, & Silvestris, 2013). For endometrial cancer, in post-menopausal obese women, higher levels of estradiol is correlated with increased risk of cancer. It appears that elevated levels of estradiol increases endometrial cell proliferation while inhibiting apoptosis, and simultaneously inducing IGF-1 synthesis in endometrial tissue (De Pergola, & Silvestris, 2013). In premenopausal women, abnormal levels of progesterone and testosterone appear to influence endometrial cancer development (De Pergola, & Silvestris, 2013).

**Hypercholesterolemia and Breast Cancer**

Breast cancer is the most common diagnosed cancer in women. Genetic mutations, increased estrogen production, diet, environmental factors, and obesity are risk factors for breast cancer (Munir et al., 2018). Hypercholesterolemia, an established co-morbidity of obesity, has also become an independent risk factor for breast cancer in postmenopausal women (Nelson et al., 2013). Hypercholesterolemia is associated with breast cancer tumor growth rate, incidence, and metastasis (Buss & Dachs, 2018, Nelson et al., 2013). Also, in mouse models, mice with hypercholesterolemia had tumors that were more proliferative, with reduced apoptosis and increased micro-vessel density (Buss & Dachs, 2018; Munir et al., 2018). An underlying mechanism that links cholesterol to breast cancer is 27-hydroxycholesterol (27-HC) (McDonnell,

Chang & Nelson, 2014; Nelson, et al., 2013). 27-HC is synthesized from cholesterol by a rate-limiting enzyme, and hypercholesterolemia results in high levels of 27-HC (McDonnell et al., 2014).

27-HC is a primary metabolite of cholesterol, and a selective estrogen receptor modulator agonist. The mammary glands, whereby one is present in each breast, are estrogen target organs, and most breast cancer has demonstrated expression of the alpha subtype of the estrogen receptor (McDonnell et al., 2014). 27-HC agonist activity has been shown to accelerate breast cancer growth and spread to the lungs. However, tamoxifen and raloxifene are anti-hormonal agents that exhibit estrogen receptor antagonist activity in breast tissue (McDonnell et al., 2014). Interventions with these agents have reduced non-invasive and invasive breast cancer in high-risk women by up to 50% (Chen, Wen, Li, Luo, & Zhang, 2016; McDonnell et al., 2014). In addition to the use of estrogen modulating agents, statins have demonstrated the ability to reduce the risk of cancer reoccurrence in breast cancer survivors (Buss & Dachs, 2018; Nelson, et al., 2013), and statins have been recommended as a therapy for preventing tumor growth rate, incidence, and metastasis in breast cancer patients with hyperlipidemia (Chen et al., 2016, Nelson, et al., 2013). Statins are lipid lowering medications, and reducing abnormally high serum lipids, such as cholesterol, can reduce its potential effects on estrogen.

**Effects of Exercise on Cancer**

Cancer is a chronic disease that is life-threatening, but for overweight and obese individuals, the risk of death is increased due to underlying mechanisms from excess adiposity that induce tumor growth, metastasis, and reoccurrence of carcinogenesis (Atretkhany et al., 2016;

Massetti et al., 2017; Zhang et al., 2018). A strong significant association between physical activity and reduced risk of bladder, breast, colon, endometrial, esophageal adenocarcinoma, renal, and gastric cancers has been demonstrated (McTiernan et al., 2019).

Exercise has demonstrated beneficial effects for prevention, treatment, and post-care treatment of cancer. It has been shown to alleviate the side effects of chemotherapy, reduce tumor aggressiveness, and it can prevent disease reoccurrence and improve mental and physical quality of life in cancer survivors (Buss & Dachs, 2018). Exercise has been shown to reduce the risk of colon, endometrial, and post-menopausal breast cancer (Andersson et al., 2019). Biomarkers of cancer that exercise has demonstrated a positive effect on are IGF-1, leptin, and C-reactive protein. High serum IGF-1 is associated with an increased risk of breast cancer development, and in a meta-analysis of randomized controlled trials of breast cancer survivors, exercise had a significant effect on reducing circulating IGF-1 levels (Fong et al., 2012). Higher levels of leptin are present in overweight and obese individuals, and high levels of leptin are associated with increased risk of breast cancer development and growth. Exercise aids in reducing excess adiposity, and reduction of adiposity has been shown to reduce serum leptin levels (Buss & Dachs, 2018). C- reactive protein is associated with decreased breast cancer survival. Exercise has demonstrated positive effects on C-reactive protein levels (Djalilova et al., 2019; Glenney et al., 2017), and most studies investigating the effect of exercise on C-reactive protein breast cancer survivors discovered decreased C-reactive protein levels in exercise groups (Buss & Dachs, 2018). Exercise could lower serum lipids, particularly cholesterol, which can reduce its underlying effects on estrogen-promoting activity that can lead to breast tumor development and growth. Exercise can mediate breast cancer development, growth, and reoccurrence though several different mechanisms, and although a specified amount has not been established, research suggests

that longer durations of exercise aid in providing beneficial effects (Buss & Dachs, 2018; Djalilova et al., 2019; Fong et al., 2012; Glenney et al., 2017). Exercise is also an effective non-pharmacological aid for treating cancer patients (Lee, Kim, & Jeon, 2018). Brown et al. (2018) found a reduction of circulating tumor cells to be associated with reductions in BMI, insulin, and soluble adhesion molecules as a result of six months of physical activity. Also, significant reductions in insulin, leptin and IL-6, and a significant increase in adiponectin have been observed in women in exercise trials (Friedenreich, 2011; Vella et al., 2017). It is evident that physical activity and exercise can improve underlying cardio-metabolic mechanisms that increase the risk of cancer, as well mediate growth and reoccurrence in obese individuals. Particularly for breast and endometrial cancer, physical activity and exercise offer promising non-pharmacological prevention and treatment for these diseases.

## Adipokines, Insulin and Their Association with the Major Diseases

Hypertension, heart disease and stroke, T2D, and cancer are major diseases that are associated with overweight and obesity. Although these diseases are distinctly characterized and defined by their symptoms, their underlying mechanisms, which stem from adipokines and insulin, are interconnected. Due to the underlying mechanisms that result from chronic inflammation of adipokines, more than one of the diseases can simultaneously manifest, and if uncontrolled without methods of treatment (e.g., medication, weight-loss, regular exercise), any remaining obesity associated diseases that have not manifested can become present and reduce an individual's quality of life, and further increase the risk of early mortality.

## Other Associated Diseases and Disorders of Overweight and Obesity

In addition to hypertension, heart disease and stroke, T2D, and cancer; non-alcoholic fatty liver disease (NAFLD), gallbladder disease, kidney disease, and depression and anxiety,

and osteoarthritis are associated with obesity. However, kidney disease commonly manifests as a secondary disease of hypertension, and depression and anxiety can manifest as a result of being overweight or obese, but it also commonly manifests as a secondary disease of heart disease and stroke, T2D, and cancer. As discussed earlier, heart disease and stroke, T2D, and cancer are chronic diseases that can have debilitating and life-threatening health effects; and these health effects increase the risk of developing depression and anxiety.

## Osteoarthritis

Osteoarthritis (OA), is a progressive and degenerative disease of the joints. It affects the articular cartilage, meniscus, ligaments, bone, and synovium (Francisco et al., 2019). It is characterized by derangement of the joints, and is facilitated by abnormal metabolism of joint tissues, cartilage degradation, bone remodeling, and osteophyte formation (Francisco et al., 2019). These derangements result in inflammation and loss of normal joint function. Osteoarthritis is the most common form of arthritis, and obese individuals are 6.8 times higher than normal-weight individuals for potentially developing knee OA (King, March, & Anandacoomarasamy, 2013).

Adiponectin and leptin are adipokines that play a role in the regulation of autoimmune and inflammatory processes that are associated with arthritic diseases (King et al., 2013). Less is known about adiponectin's role in OA; but pro-inflammatory and anti-inflammatory properties have been reported in adiponectin. However, both adiponectin and leptin are significantly elevated in individuals with OA (King et al., 2013). Leptin has demonstrated increased levels of degradative enzymes, such as matrix metalloproteinases (MMPs) and nitric oxide; which play a role in the degradation of the cartilage, synovium and bone tissues of the joints (King et al., 2013).

### Women and Knee OA

Women are more impacted by knee OA than men. Some contributing factors are anatomic and hormonal differences. Anatomical differences are narrower femurs, thinner patellae, larger quadriceps angles, and differences in tibial condylar size (Hame & Alexander, 2013). Postmenopausal women are at increased risk of developing arthritis, which is linked to a decrease in estrogen (Hame & Alexander, 2013). These conditions lead to women having more severe OA than men. This results in a greater need for pharmacological treatment, physical therapy treatment and treatment with knee braces, and knee replacement surgery for women (Hame & Alexander, 2013).

### The Effects of Exercise on OA

Exercise promotes weight-loss, and because excess weight increases joint stress, exercise can aid in relieving joint stress by reducing body weight. Exercise also aids in muscle strengthening of the joints, which relieves OA pain (Villafañe, 2018). In addition, a combination of exercises such as combined strength, flexibility, and aerobic exercises are most beneficial for relieving OA pain and disability (Villafañe, 2018).

## Non-Alcoholic Fatty Liver Disease and Gall Bladder Disease

The prevalence of NAFLD is estimated to be more than 25% in obese individuals in the U.S. Globally, the prevalence if NAFLD increases in T2D (70%), and morbid obesity (90%) due to its association with obesity and metabolic syndrome (Ahmed, 2015). NAFLD is an accumulation of fat in the liver in individuals who drink little to no alcohol. Insulin resistance is thought to be responsible for the development of NAFLD, because insulin suppresses lipolysis in adipose tissue. Lipolysis increases plasma FFA, which results in an influx of FFA into the hepatocytes (Ahmed, 2015).

Gall bladder disease also results from hyper-lipid accumulation. Gallstones are a common diagnosis of gall bladder disease. Gallstones are hardened deposits of digestive fluid that contains highly concentrated cholesterol bile (Afamefuna & Allen, 2013). The hyper-saturation of cholesterol in the bile is primarily due to hypersecretion of cholesterol from the liver due to altered hepatic cholesterol metabolism (Afamefuna & Allen, 2013; Chang et al., 2015). The altered hepatic cholesterol metabolism is attributed to insulin resistance, dyslipidemia, and cardiovascular disease. Gallbladder disease appears to be a secondary disorder of NAFLD and metabolic dysfunctions of obesity, affecting more than 20 million Americans each year (Afamefuna & Allen, 2013; Vita et al., 2010). The occurrence of NAFLD and gallbladder disease do not significantly differ in women and men, however exercise can be used to aid in preventing and treating the diseases. The effects of exercise on lipids, as discussed in the major health disorder sections, are synonymous for averting underlying lipid-related mechanisms that lead to NAFLD and gallbladder disease.

## Kidney Disease

Kidney Disease is damage to the kidneys that has resulted in inadequate filtering of the blood. Acute kidney injury is a sudden and temporary loss of kidney function, and chronic kidney disease (CKD), which has five stages that range from kidney damage with normal kidney function to end-stage kidney failure and is a gradual loss of kidney function over time. Over several years, CKD can lead to end-stage kidney failure, which requires dialysis or a kidney transplantation for survival (Hemmelgarn et al., 2012). High blood pressure and diabetes are each a main cause of CKD, and almost half of the individuals who have CKD have diabetes and/or CVD. Being overweight or obese increases the risk of developing CKD indirectly through diabetes, CVD, and hypertension. However, the underlying inflammatory effects of excess adiposity

(insulin resistance, renin-angiotensin-aldosterone system activation, oxidative stress, and abnormal lipid metabolism) that also lead to development of T2D, CVD, and hypertension, can directly affect the kidneys (Kovesdy, Furth & Zoccali, 2017). The inflammatory effects of excess adiposity results in pathological changes to the kidneys that include ectopic lipid accumulation and increased deposits of renal sinus fat, and the development of glomerular hypertension and increased glomerular permeability (Kovesdy et al., 2017). These pathological changes can ultimately lead to glomerulosclerosis, which is hardening of the glomeruli (small blood vessels) in the kidneys (Kovesdy et al., 2017). These direct and indirect effects of excess adiposity on the kidneys explain how obesity is a potent risk factor for CKD.

**Women and CKD**

Statistically, 14% of the U.S. population has CKD. Males have slightly higher mortality rates than females, however women are more likely to have stages one through four (stage four being severe loss of kidney function) of CKD than men (Xu et al., 2016). This is of special concern, particularly for women who are pregnant and have pre-existing CKD. Under these conditions, pregnancy worsens hypertension and proteinuria. Also, preeclampsia occurs in one third of pregnant women with mild CKD. CKD increases the risks of premature birth, low birth weight, and fetal death; and the risks of these fetal conditions increase with moderate and severe CKD, and end-stage kidney disease (Bili, Tsolakidis, Stangou & Tarlatzis, 2013). In addition to pregnancy complications, women with CKD experience more incidents of complications from dialysis than men, and women are less likely than men to be kidney transplant recipients (Piccoli et al., 2018). Because of the effects that CKD has on pregnancy, and the hardships that women experience from treatment, CKD presents very extreme outcomes that can chronically reduce quality of life in women who are plagued by this disease.

## Depression and Anxiety

Depression is a state of having a sad mood for a long period of time, and it interferes with normal-everyday functioning. Anxiety is excessive worry that is constant or worsens over time. Although they are distinct psychological disorders, it is common for an individual with an anxiety disorder to also suffer from depression or vice versa (Brody, Pratt & Hughes, 2018).

Depression and anxiety in relation to chronic disease are thought to stem from and individual's quality of well-being. Chronic disease can negatively affect health-related quality of life (HRQOL) (Megari, 2013). HRQOL is an individual's perceived quality of well-being or lack thereof. HRQOL broadly consists of physical, psychological, and social functioning that are affected by an individual's disease and/or treatment (Megari, 2013). Lack of quality of well-being can lead to depression and anxiety; and the effects of chronic diseases such as CKD, heart disease, stroke, T2D, and cancer attribute to cases of depression and anxiety (Heyworth, Hazell, Linehan, & Frank, 2009; Megari, 2013).

Overweight and obesity are also chronic conditions that are associated with depression and anxiety. Their association with depression and anxiety are commonly related to body dysmorphic disorder (BDD), negative social interaction and discrimination; which are physical, psychological, and social dysfunctions that reduce quality of life (Griffiths, Jenkins, & Castle 2017; Wu & Berry, 2018). BDD, which is a state of having markedly excessive body dissatisfaction or displeasure, is a distress that leads to concerns of being rejected by others, and impairment in one or more areas of social, occupational, academic, and role functioning (Knight, 2011). Therefore, the psychological effects of excess body weight can be detrimental to an individual's function in personal and professional relationships, which can hinder normal life progression and in extreme cases, result in suicidal behavior.

The relationship between depression and anxiety, and excess body weight is bidirectional. Although excess body weight can lead to depression and anxiety, it can lead to additional weight-gain. 43% percent of adults with depression are obese, and adults with depression are more likely to become obese than adults without depression (Pratt & Brody, 2014). For example, depression and anxiety have been shown to lead to food binging, which can cause excess weight-gain (Schulz & Laessle, 2010). For an individual who is already overweight or obese, if they become depressed, binge-eating can further exacerbate their weight condition and worsen the depression.

In addition to binge-eating, underlying metabolic pathologies that are related to excess adiposity also contribute to weight-gain. Dysregulation of leptin and insulin contribute to increased hunger (Japur et al., 2019). Leptin promotes satiety, but excess adiposity dysregulates leptin and causes reduced satiety. The reduction in satiety results in increased appetite that leads to weight-gain (Hart, 2018; Mills, Thomas, Larkin, Pai, & Deng, 2018). Appetite and weight-change are central to major depressive disorder, and leptin has been positively correlated with problematic eating behaviors in overweight adults (Mills et al., 2018). Insulin primarily regulates glucose metabolism and energy homeostasis. Energy homeostasis aids in appetite control, and due to insulin resistance that occurs in obesity, the appetite-control effect of insulin is diminished (Alsaadi, & Van Vugt, 2015; Han et al., 2008). Although a direct relationship between depression and anxiety, and leptin and insulin has not been widely studied, the positive correlation between increased appetite and metabolic dysregulation has been well-established, and this interaction contributes to weight-gain and/or lack of successful weight-loss that can promote depression and anxiety.

## Women and Depression

Depression among women is a serious health concern because women (10.4%) are almost twice as likely as men (5.5%) to have depression (Brody et al., 2018). Depression in women is associated with hormonal changes that occur from puberty to menopause, with postpartum depression occurring in 10-15% of women (Brody et al., 2018). In addition to biological changes, unequal power and status that can create uncertain financial security and lack of access to resources, overwhelming responsibilities of both work and family, and sexual or physical abuse are associated with depression in women (HHS, 2015). As discussed earlier, depression can lead to weight-gain that results in becoming overweight and/or obese or worsen either condition. Due to women being twice as likely as men to have depression, weight-control may be more difficult for women due to the contribution of depression and anxiety, and investigations are needed in order to determine if depression is a significant contributing factor.

## Effects of Exercise on Depression and Anxiety

Exercise is a non-pharmacological method for treating depression and anxiety, and at least 30 minutes per day of physical activity is recommended for prevention (HHS, 2015). Patients in an aerobic training program have been shown to be less likely to relapse than patients assigned to receive medication, and a significant reduction in medication dose has been reported for patients who exercised (Ranjbar et al., 2015). Inadequate symptom management, unacceptable side effects, and inadequate methods for coping are commonly reported in clinically depressed patients. However, exercise provides an alternative for treating depression as it does not result in side effects such as weight-gain, insomnia, or symptoms of withdrawal that result from pharmacological therapy (Moraes, Miranda, Loures, Mainieri & Mármora, 2018; Ranjbar et al., 2015). In addition to not resulting in side effects, exercise has demonstrated an ability to mediate

underlying biological mechanisms that facilitate depression and anxiety. Exercise has been associated with decreasing depression-related pro-inflammatory cytokines (TNF-$\alpha$; IL-1β; and IL-6) and hormones [adrenocorticotropic hormone (ACTH) and cortisol]; and exercise is associated with increasing hormones and neurotransmitters [norepinephrine, serotonin, endorphins, brain-derived neurotrophic factor (BDNF), and endocannabinoids] that regulate stress response and mood. Regulation of these hormones produce anti-depressive and anxiolytic behavioral responses (Moraes et al., 2018; Ranjbar et al., 2015).

Also, particularly for women, a positive relationship exists between exercise and ovulation, and this may provide indirect anti-depressive and anti-anxiety effects due to exercise's ability to regulate metabolic function (Hakimi & Cameron, 2017). Polycystic ovarian syndrome (PCOS) is a chronic metabolic disorder that is associated with overweight and obesity. Infertility, due to anovulation, is one of the symptoms of PCOS (Hakimi & Cameron, 2017). Anovulation accounts for about 30% of infertility cases, and it severely effects women in terms of depression and anxiety (Hakimi & Cameron, 2017). However, exercise offers beneficial effects in terms of improving metabolic health for women with PCOS, and it may aid in relieving the symptom of infertility, which can make infertility less of a contributing factor of depression and anxiety in women. There is also a prevalence of depression that exists in older women and women of mid-life stage. Changes in sex hormones, due to the phases of menopause (perimenopause, menopause, and post-menopause), cause chronic physical symptoms and changes in mood (Clayton & Ninan, 2010). Some commonly reported symptoms are severe hot flashes and night sweats, sexual discomfort, urinary incontinence, weight-gain, hair-thinning, and sleep disturbance. The emotional and physical changes that occur during the phases of menopause have been associated with inducing depression and anxiety (Clayton & Ninan, 2010). However, a 12-week exercise

intervention demonstrated improvements in sleep quality, insomnia and depression in women of midlife (Sternfeld et al., 2014). Also, a meta-analysis of exercise interventions of six or more weeks, demonstrated that exercise significantly reduces depressive symptoms, and less perceived stress and insomnia after bouts of exercise were discovered as secondary outcomes in midlife and older women (Pérez-López, Martínez-Domínguez, Lajusticia & Chedraui, 2017). For women who experience depression and anxiety during the phases of menopause, exercise can be used as an effective therapy to reduce depression and anxiety symptoms.

### The Big Three in Obesity: The Effects of Adiponectin, Leptin, and Insulin

Each disease and disorder that is associated with overweight and obesity (hypertension, heart disease and stroke, T2D, and cancer; NAFLD, gallbladder disease, and osteoarthritis) manifests, in part or in combination, from decreased adiponectin and increased leptin, and increased insulin. These pro-inflammatory markers and metabolic marker of overweight and obesity mechanistically lead to the different diseases, but their pathological origins primarily explains why multiple morbidities exist in overweight and obese individuals, and it explains why having one disease increases the risk of developing another (e.g., T2D and its association with heart disease). In addition, because adiponectin and leptin have central roles in regulating satiety, alterations in their activity have demonstrated an association with increased appetite (Blüher, 2012). Also, insulin resistance has a negative effect on satiety. Insulin resistance hinders glucose from entering the cells, resulting in the cells being unable to convert glucose to adenosine triphosphate (ATP) for use as energy. The lack of available energy, caused by insulin resistance, results in an increase of hunger, which is also known as polyphagia (Balaji, Duraisamy, & Kumar, 2019). Increased appetite can lead to additional weight-gain or extreme difficulty with weight-loss, which severely effects overweight and obese individuals. The underlying disease-related mechanisms

of adiponectin, leptin and insulin and their negative impact on satiety both centrally explain the seriousness of obesity. In addition, leptin and insulin appear to have an interactive relationship as they have been reported as having the ability to directly regulate one another (Amitani et al., 2013; Paz-Filho et al., 2012). Further research must be completed in order to fully establish how this relationship impacts obesity-related diseases. However, both are consistently reported as underlying mechanisms of dyslipidemia.

## Leptin and Insulin: Their Connection with Dyslipidemia

In addition to being underlying mechanisms of heart disease, stroke, T2D, cancer, NAFLD, gallbladder disease, and osteoarthritis; increased leptin (hyperleptinemia), and increased insulin (hyperinsulinemia) are also underlying mechanisms of dyslipidemia. Dyslipidemia directly impacts the etiology of the obesity-related diseases. As discussed earlier, hyperleptinemia is an underlying mechanism of atherosclerotic plaque (Alpert et al., 2018; Ellulu, et al., 2017; Wende et al, 2012), which leads to heart disease and stroke. Hyperinsulinemia is an underlying mechanism of cardiomyocyte lipotoxicity and atherosclerotic plaque that results from increased triglycerides and free-fatty acids (Alpert et al., 2018; Razani et al., 2008; Wende et al, 2012). Cardiomyocyte lipotoxicity and atherosclerotic plaque lead to heart disease and stroke. In addition, the increase in triglycerides and free-fatty acids is also associated with T2D (Ormazabal et al., 2018; Schofield et al., 2016), and increased free-fatty acids lead to NAFLD and gallbladder disease (Ahmed, 2015). Breast cancer is also affected by dyslipidemia, namely hypercholesterolemia. An independent association between hyperinsulinemia and hypercholesterolemia has not been exhibited (Ormazabal et al., 2018), but hyperinsulinemia has exhibited an association with familial lipids such as increased triglycerides and LDLs (Ormazabal et al.,

2018). Also, findings from a recent meta-analysis suggests that triglycerides, but not total cholesterol and LDLs, have an inverse association with breast cancer risk (Ni, Liu, & Gao, 2015). Therefore, in addition to cholesterol, LDLs appear to be associated with breast cancer, and because hyperinsulinemia has demonstrated an association with this lipoprotein, the effects of hyperinsulinemia on LDLs may play a role in the development of breast cancer.

## Women's Health in the Obesity Epidemic

The serious health consequences that arise as a result of excess adiposity are detrimental and can become life threatening. Women are impacted by these diseases differently than men in terms of morbid prevalence, treatment, and death. Women present a higher prevalence of hypertension than men (Xiao et al., 2019), which is partly due to lack of vasodilation that occurs as a result of decreased estrogen in older women (Briant, et al., 2016; Papakonstantinou et al., 2013). For CVD, women have higher perioperative mortality and higher periprocedural complication rates than men (Papakonstantinou et al., 2013). Also, due to differences in heart and vasculature size, fat mass and body fat distribution (Elffers et al., 2017; Schorr et al., 2018), and neuro-hormonal and inflammatory markers (Lew et al., 2017), CVD poses serious detrimental health risks in women. Women are also significantly impacted by stroke. Almost 60% of stroke-deaths are in women, and stroke kills twice as many women as breast cancer (Benjamin et al., 2019). Regarding T2D, women have a higher risk of T2D-related CVD complications, blindness and depression than men (Pan, et al., 2010). Women who develop gestational diabetes, develop T2D within five to ten years postpartum (Herick et al., 2019; Nabuco et al., 2016), and older women are at greater risk of developing T2D than older men due to metabolic disorders associated with menopause (Stachowiak, Pertyński & Pertyńska-Marczewska, 2015). Post-menopausal women are at higher risk of developing breast cancer due to the bioactivity of estrogen and higher levels of

other sex steroids (Bhardwaj et al., 2019; De Pergola, & Silvestris, 2013; Strong et al., 2015). Also, endometrial cancer is prevalent among post-menopausal, and pre-menopausal women can have increased risk due to abnormal levels of progesterone and testosterone (De Pergola, & Silvestris, 2013). The impact of knee OA is more severe for women than men. Contributing factors are anatomic and hormonal differences that lead to the need for more aggressive treatment (Hame & Alexander, 2013). CKD impacts women differently than men due to pregnancy and fetal complications (Bili et al., 2013); women experience more incidents of complications from dialysis, and women are less likely than men to be kidney transplant recipients (Piccoli et al., 2018). Women are almost twice as likely as men to experience depression in each phase of life (adolescence to post-menopause), which is partly attributed to biological changes, weight-control difficulty, socioeconomic factors, and abuse (Brody et al., 2018). Solutions to the obesity epidemic, particularly for women are needed.

## Intensive Lifestyle Interventions for Treating the Obesity Epidemic: Their Evolution, Their Impact on Research, and Walking as a Practical Modality

For several decades, researchers have sought intervention solutions for the obesity epidemic. Behavioral treatments for obesity have been drastically studied, and under several iterations they have been refined in an effort to obtain solutions for combatting such a chronic epidemic (Williamson, 2017). In 1967, the first paper was published to describe behavioral treatment for overeating in obese individuals (Stuart, 1996). The study was comprised of eight patients, who were women, being treated for obesity over a 12-month period. The paper reported their weight-loss results as well as possible confounding factors, and changes in social interactions. Fifty years later, behavioral treatment research evolved into large cohort multi-site studies

funded by the National Institute of Health (NIH) that focused on intensive lifestyle interventions (ILIs). The ILIs include a calorie-restricted dietary component, group therapy, health education, and exercise prescription (Williamson, 2017). The first implementation of the large ILI studies was the Diabetes Prevention Program (DDP) in 1994, and it was later published in 2002 (Williamson, 2017). Next the Look AHEAD ILI emerged in the early 2000s, followed by the POUNDS Lost study, and then the CALERIE study (Williamson, 2017). Although there are several other ILI experiments that exist, these four studies built upon one another; and collectively they demonstrated moderate, but clinically relevant weight-loss and improved health among their participants (Williamson, 2017).

The studies ranged from 225 to 5145 participants, with most participants in all the studies were women (≥61%). For the exercise component of ILIs, two of the four studies specifically recommended walking or counting steps as a modality for their exercise prescription. The DPP recommended brisk walking as a modality for reaching the activity goal of 150 minutes per week (Diabetes Prevention Program Research Group, 2002). Their recommendation of walking was based on a previous clinical trial that used walking to successfully reach the physical activity goals among older women (Pereira et al., 1998). Look AHEAD advised their participants to strive for >10,000 steps per day by the final phase of their program. Their recommendation was built from the DPP's intervention method, and it was based on a study that demonstrated daily walking can be used as a modality of exercise as part of a weight-loss and health improvement program (Yamanouchi et al., 1995). The remaining two studies, CALERIE and POUNDS Lost, included physical activity recommendations such as minutes per week, but they did not indicate if specific modalities were recommended (Rochon et al., 2011; Sacks et al., 2009). While the fo-

cus of this study is not on the practice of ILI research for obesity, the four major studies represent an area of research that has made strides toward combatting the obesity epidemic, and they provide a blueprint of interventional methods for successful weight-loss and health improvement. Their use of walking for achieving weekly exercise goals among the intervention groups demonstrated that this modality of exercise is effective for improving health in overweight and obese adults. In addition, the population majority among the studies were women, which implies that women benefit from using walking as an exercise modality to effectively meet weekly physical activity goals. This implication lends to investigating walking for its effectiveness for improving health in overweight and obese women.

From the review of literature, dyslipidemia is a risk factor and comorbidity of the major diseases (heart disease, stroke, T2D, cancer) that are associated with obesity. Dyslipidemia contributes to the etiology of these diseases, which explains it association. Dyslipidemia's contribution to these diseases results from pro-inflammatory and metabolic abnormalities of hyperleptinemia and hyperinsulinemia (Amitani et al., 2013; Paz-Filho et al., 2012). Therefore, because walking has been practically used as an exercise modality in major obesity-related health interventions, statistically analyzing its effectiveness on lipids in women is warranted.

## The Impact of Weight-Loss Interventions on Lipids

Similar to the ILIs, weight-loss interventions have demonstrated the ability to improve lipids in overweight and obese adults. Changes in lipids have been observed in diet-only and diet and exercise interventions. Diet-only interventions consisted of 55% carbohydrate, 15% protein and 30% fat (Namjou et al., 2017), hypocaloric (< 1400 calories per day) and high protein diets (Meckling & Sherfey, 2007), and a 500 to 1,000 calorie reduction per day (Fayh, Lopes, Silva, Reischak-Oliveira, & Friedman, 2013). The interventions significantly reduced total cholesterol

(Fayh et al., 2013; Meckling & Sherfay, 2007), triglycerides (Fayh et al., 2013; Namjou et al., 2017), and LDLs (Meckling & Sherfay, 2007). Also, when diet plus exercise interventions were compared to diet-only interventions, each of the lipid observations (total cholesterol, triglycerides, and LDLs) significantly improved, but weight-loss was a congruent result of the diet-only and diet plus exercise interventions (Fayh et al., 2013; Meckling & Sherfay, 2007; Namjou et al., 2017). In other weight-loss studies that evaluated diet plus exercise interventions that focused on specific exercise modalities (≥ 10 minute bouts, interval training, walking, leisure and occupational activities) with moderate or vigorous intensities; total cholesterol, triglycerides, LDLs (Jakicic et al., 2015; Kirkwood, Aldujaili & Drummond, 2007; Kuller et al., 2012; Mora-Rodriguez et al., 2016), and HDLs (Brown, Swendener, Shaw, & Shaw, 2010) significantly improved along with weight-loss and improvements in body composition. These findings demonstrate that weight-loss that is produced by either diet-only or diet plus exercise can significantly improve lipids. In addition to weight-loss improving lipids, it also improves other metabolic syndrome factors in overweight and obese adults.

## Weight-Loss, Weight Regain, and Weight Maintenance

Metabolic syndrome is a group of risk factors that increase the likelihood of developing heart disease, diabetes, and stroke (Thomas et al., 2010). The risk factors are high triglycerides, low HDLs, high blood pressure, high blood sugar, and excess fat around the waist (Mora-Rodriguez et al., 2016). Overweight and obese adults are more likely to develop metabolic syndrome than normal weight adults (Bradshaw, Monda, & Stevens, 2013). Weight-loss of at least 5% has positive effects on metabolic syndrome risk factors (Karppinen et al., 2016), particularly lipids (Ryan, Serra, & Goldberg, 2018). And even with modest weight-regain, lipid improvements have

remained constant (Ryan et al., 2018). However, with 30% and 50% weight-regain, lipid improvements have been shown to regress back to baseline values (Beavers D. P., Beavers, K. M., Lyles, & Nicklas, 2013; Thomas et al., 2010). Unfortunately, most adults regain almost half of their weight within two years (Ryan et al., 2018), and almost all weight within three to five years (Dulloo & Montani, 2015; Ryan et al., 2018). And although it has also been suggested that individuals' transition from weight-loss to a period of weight maintenance, and then progressive weight-regain, Ross, Qiu, You, and Wing (2018) confirmed that progressive weight-regain occurs after weight-loss with no period of maintenance.

Overweight and obese individuals commonly make numerous attempts at weight-loss, and even with successful attempts, the possibility of weight-regain is inevitable, especially without an intervention of post-weight-loss care (e.g., individual or group behavioral support) (Ross et al., 2018). Repeated periods of weight-loss and regain are cyclical weight fluctuations that can lead to altered hormonal balance and cause poor homeostasis of energy and decreased resting metabolic rate (Nozari, 2018). Each of these factors make it more difficult to lose weight and easier to regain weight than previous attempts (Nozari, 2018). In addition, cycling of weight-loss and regain increases health risks for metabolic syndrome, hepatic steatosis, bone fracture, cardiovascular disease, and cancer (Nozari, 2018). In addition to physiological disorders, weight regain after weight-loss can negatively affect individuals psychologically, making long-term changes in health behavior more difficult.

Behaviors such as disinhibition of eating, grazing on food throughout the day, food cravings, lack of exercise, and not following post-intervention recommendations as well as psychological factors such as poor self-esteem, and lack of social support all contribute to weight regain (Bond, Phelan, Leahey, Hill & Wing, 2009; Geraci, Brunt, & Hill, 2015). In addition, emotional

regulation has also been associated with weight regain, and it has been identified as a skill that is needed for improving weight maintenance after weight-loss (Sainsbury, 2018).

Long-term weight maintenance after weight-loss is multifaceted in terms of physiological processes and psychological factors that affect behavior. Consuming a balanced diet and regular physical activity play an important role in homeostasis of energy and increased resting metabolic rate. Successful weight maintenance, in regard to behavior, includes adjusting diet and exercise behavior, regular monitoring of fluctuations in weight and taking immediate action when there is weight-gain, and having strategies for coping with life events (Chambers & Swanson, 2012). Consistent and long-term collective management of these tasks can be a daunting lifestyle adjustment. However, consistent focus on modifying one of the behaviors that promote weight-maintenance (e.g., diet or exercise) may lead to greater success of weight-loss maintenance and long-term improvements of overall individual health (e.g., reduction of cardio-metabolic risk factors). Maruthur et al. (2014) determined from their systematic review of non-weight-loss focused interventions, that self-management ("problem-solving, addressing barriers, self-monitoring, goal-setting, and individualized counseling") and exercise prevents weight-gain and increases in BMI and waist circumference, and promotes reductions in LDLs. Fanning et al. (2018) demonstrated that the addition of exercise in a weight-loss intervention resulted in improved health-related quality of life and exercise self-efficacy, which are related to successful weight maintenance. Also, a 12-week moderate to vigorous aerobic exercise intervention used to promote weight maintenance after ≥5% weight-loss demonstrated a significant increase in exercise and exercise acceptance (Butryn, Kerrigan, Arigo, Raggio, & Forman, 2018).

For overweight and obese individuals, weight-loss is the optimal approach to improving health by reducing cardio-metabolic risk factors, particularly the elimination of abnormal lipids.

Health improvements are also sustained by maintaining a healthier weight. However, because individuals experience weight regain of almost all weight that has been lost within three to five years (Dulloo & Montani, 2015; Ryan et al., 2018) and successful weight maintenance requires consistent management of collective behaviors (Chambers & Swanson, 2012), a lifestyle that focuses on improving or maintaining other health biomarkers, such as lipids, may be more beneficial. Regain of weight that has been lost can be discouraging and this can lead to dismissal of lifestyle practices (e.g., consistent consumption of a healthy diet and regular exercise) that once facilitated the weight-loss. If overweight and obese individuals are encouraged to exercise regularly in order to improve or maintain improved lipids, morbidity and mortality from dyslipidemia's associated diseases (heart disease, stroke, T2D, cancer) may be prevented.

## Effects of Exclusive Exercise Interventions on Lipids

### Aerobic Exercise Interventions: Implications for Duration, Volume, and Intensity

In overweight and obese adults, the effects of exclusive exercise on lipids has been tested in short-and long-term sessions. Three consecutive days of moderate to vigorous exercise decreased triglycerides and increased HDLs (Wagganer, Robison, Ackerman, & Davis, 2015), four weeks of exercise decreased LDLs (Mahdirejei, Berarei, Farzanegei, & Ahmadi, 2014), and 12 months of physical activity decreased LDLs and total cholesterol (Choo et al., 2010). In studies that examined the effect of exercise on lipids with non-traditional methods of aerobic activity, a mini trampoline rebound 12-week exercise program decreased LDLs and triglycerides and increased HDLs (Nuhu & Maharaja, 2018). Also, adults who practiced yoga twice per week for more than a year decreased their LDLs (Pastucha et al., 2012). In a review of moderate to vigorous aerobic exercise experiments that ranged from 12 to 24 weeks, HDLs, LDLs, and triglycer-

ides improved, with the greatest improvements in each of these lipid parameters in a 24-week experiment (Yating & Danyan, 2017). In addition, the results of the studies suggested that exercise duration, volume, and intensity all effect changes in lipids (Yating & Danyan, 2017). Yating and Danyan (2017) also concluded that exercise aids in preventing and treating dyslipidemia and it reduces the risk of myocardial infarction and coronary artery disease. Clinicians should encourage as much exercise as possible in their patients. In a systematic review, the effects of exercise interventions on lipids were analyzed and exercise resulted in moderate to strong effects for reducing total cholesterol, triglycerides and LDLs, and increased HDLs (Glenney et al., 2017).

## Walking Interventions in Overweight and Obese Women

### Implications for walking volume and duration.

For overweight and obese women with dyslipidemia, aerobic exercise demonstrated improvements in total cholesterol, triglycerides, LDLs, and HDLs (Baharloo, Taghian, & Hedayati, 2014; Costa et al., 2018; Lee, Kim, J. H., Kim, J. W., & Kim, D.Y., 2017) in pre-menopausal (Costa et al., 2018) and post-menopausal women (Lee et al., 2017); and in women with hypothyroidism (Baharloo et al., 2014). Also, in a six-month walking program where elderly obese women walked three times per week for 50 minutes, triglycerides and total cholesterol decreased, and HDLs increased (Sung & Bae, 2012). Walking programs and interventions that meet recommended physical activity intensity, frequency, and duration (ACSM, 2014) have demonstrated beneficial effects on lipids in overweight and obese women (Arija et al., 2017; Garnier et al., 2015; Hagner-Derengowska et al., 2015; Skogstad et al., 2016). Moderate to vigorous walking intensity resulted in decreased cholesterol, LDLs (Arija et al., 2017; Garnier et al., 2015) and triglycerides, and increased HDLs (Garnier et al., 2015). Also, cholesterol and LDLs decreased in participants who walked most days of the week (Skogstad et al., 2016). In a 10-

week walking program where individuals participated in the activity for 60 minutes most days of the week, all measures of lipids improved (cholesterol, triglycerides, LDLs, and HDLs) (Hagner-Derengowska et al., 2015) and in a nine-month walking intervention, total cholesterol and LDLs improved (Arija et al., 2017). In a two-year follow-up of the nine-month intervention, the intervention group had significantly lower incidence of adverse cardiovascular events than the control group, and the intervention group adhered to regular physical activity significantly more than the control group (Arija et al., 2017). Results from these studies suggest that walking interventions are effective for improving all lipids parameters in overweight and obese women. Interventions over several weeks and months that prescribe walking most days of the week appear to lead to improving all the lipid parameters.

**Implications for walking intensity.**

CVD, stroke, and cancer are each affected by dyslipidemia. Therefore, it is important to know how well intensity improves the lipid parameters (cholesterol, triglycerides, LDLs, and HDLs). Hagner-Derengowska et al. (2015) demonstrated that all lipid parameters were improved in a program that met physical activity frequency and duration recommendations. However, the intensity of their program was not clearly indicated in the study, and they utilized Nordic walking for their intervention. Nordic walking is a combination of walking and use of poles that push oneself over the ground. It is designed to use 90% of muscles in the body and strengthen the upper body muscles in order to increase mobility of the upper spine (Hagner-Derengowska et al., 2015). As opposed to general walking without the use of equipment that generates additional body weight resistance, Nordic walking combines walking with equipment that is designed to also strengthen and incorporate use of more muscles, which may further increase lipid metabo-

lism. Therefore, this study did not determine the effectiveness of walking solely as an aerobic activity for improving lipids, and in it is important to know how aerobic intensity effects lipids in this population.

Moderate to vigorous physical activity intensity is recommended for general health benefits (ACSM, 2014). Hamer, Stamatakis, and Steptoe, (2014) compared low-intensity to moderate-vigorous intensity walking in overweight adults, and moderate to vigorous walking intensity was associated with health risk factors and improvements in triglycerides and HDLs. In non-weight-loss focused experiments, where walking was exclusively used to determine its effects on lipids in overweight and obese women, no significant improvement with moderate walking intensity (60-70% $\dot{V}O_{2\ max}$) in total cholesterol, triglycerides, LDLs (Vega-López et al., 2015; Wooten et al., 2011), and HDLs (Wooten et al., 2011) was demonstrated. However, in a 12-month walking program, HDLs were significantly improved with slightly different moderate walking intensity (50-60% $\dot{V}O_{2max}$) (Vega-López et al., 2015). Vigorous walking intensity (70%≤ $\dot{V}O_{2max}$) demonstrated significant improvement in total cholesterol, LDLs, and triglycerides (Buyukyazi, 2008), and combined moderate and vigorous walking intensity (50-75% HRR) demonstrated significant improvement in total cholesterol (Mezghanni et al., 2014). In these experiments, lipids at baseline varied (e.g., normal versus abnormal) and the study design for each experiment was different regarding intervention timeframe and walking intensity. For example, no significant changes in total cholesterol, HDLs, LDLs, or triglycerides were demonstrated in participants with normal lipids at baseline (Wooten et al., 2011), but significant changes were demonstrated in experiments with participants who had abnormal or combined (normal and abnormal) lipid status at baseline (Buyukyazi, 2008; Mezghanni et al., 2014). The experiments

ranged from a single-bout intervention (Wooten et al., 2011) to several weeks of activity (Buyukyazi, 2008). However, moderate walking intensity demonstrated significant improvement in HDLs (Vega-López et al., 2015), but no significant improvement in total cholesterol, LDLs, and triglycerides (Vega-López et al., 2015; Wooten et al., 2011). Vigorous and combined (moderate and vigorous) walking intensity also demonstrated significant improvement in total cholesterol, LDL, and triglycerides (Buyukyazi, 2008; Mezghanni et al., 2014). In overweight and obese women, it appears that HDLs are significantly improved with moderate walking intensity, however combined or vigorous walking intensity appears to be necessary in order to significantly improve total cholesterol, triglycerides, and LDLs.

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# II THE EFFECTS OF WALKING ON SERUM LIPIDS AND LIPOPROTEINS IN OVERWEIGHT AND OBESE WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS

## Statement of Research Question

Physical inactivity is more common among women than men (CDC, 2018) and two-thirds of women are overweight and obese (U.S. Department of Health and Human Services, 2017). Because the prevalence of dyslipidemia is highest among overweight and obese adults (Saydah et al., 2014), physical activity interventions that focus on improving lipids and lipoproteins may be effective for reducing CVD among women. Interventions that have focused on weight-loss have demonstrated improved lipid and lipoprotein profiles in overweight and obese women (Fayh et al., 2013; Namjou et al., 2017). However, significant weight-loss and weight-loss maintenance are difficult due to several physiological and psychological factors (APA, 2018; CDC, 2017a). Improving a single lifestyle habit, such as increasing physical activity, can be more beneficial for improving overall health (particularly improving lipids and lipoproteins) as opposed to the negative effects of cyclical weight-loss and regain that results from attempts to manage multiple lifestyle adjustments (Nozari, 2018). Walking is a simple and safe exercise (AHA, 2017), and because it is simple and safe, it is easier to adopt as a long-term exercise habit than other forms of exercise that require equipment (e.g., elliptical training, bike riding, circuit weight-training) or demand more coordinated movement (e.g., group exercise focusing on dance). Walking has also been demonstrated as a practical exercise modality for improving health in large intensive lifestyle interventions (ILIs). In addition, walking can have secondary

positive psychological and social effects because it can be enjoyed in outdoor environments (e.g., natural ambiance of a park or walking trail), and with friends or family.

Research that has investigated the exclusive effects of walking on lipids and lipoproteins in overweight and obese women has demonstrated some improvement, but the results varied. Lipid and lipoprotein values were improved in some studies and not in others, and exercise intensity and duration appeared to moderate lipid and lipoprotein results. Completing a meta-analysis provides a better estimate of the effects of walking on lipids and lipoproteins than a single experiment. Previous meta-analyses that have calculated the effects of walking on lipids and lipoproteins were not limited to experiments of overweight and obese adults, they did not consistently analyze the moderating effects of intensity and duration, and they were not limited to women. However, women are more likely than men to die from their first myocardial infarction, women who survive their first coronary event are twice as likely to subsequently develop heart failure or have a recurrent coronary incident, and women have at higher risk for stroke than men (Cífková and Krajčoviechová, 2015). Therefore, primary prevention is especially critical for this population. Regular physical activity is a method of primary prevention that's advised by clinicians for preventing cardiovascular disease (Arnett et al., 2019). Completing a meta-analysis on the effects of walking on lipids and lipoproteins for women who are at higher risk of developing cardiovascular disease, due to excess body weight, is warranted.

Due to the varied results that exists among exclusive walking experiments with overweight and obese women, does the exclusive form of walking exercise have a significant effect on lipids and lipoproteins in overweight and obese women, and does exercise intensity and duration moderate lipids and lipoproteins in this population?

## Purpose Statement and Hypotheses

The purpose of this study was to complete a systematic review and meta-analyses to determine if walking has a significant effect on lipid and lipoprotein profiles in overweight and obese women, and to determine the moderating effects of walking intensities (moderate and vigorous) and duration on lipids. The meta-analyses were used to statistically combine data from experiments that investigated changes in lipids and lipoproteins in walking interventions for overweight and obese women. The treatment effect (raw mean difference) from each study included in the meta-analyses were used to identify a common effect. Also, sub-group and meta-regression analyses were used to determine the effects of moderator variables. The meta-analyses were used to determine or further validate implications for exercise prescription that are used to normalize lipids and lipoproteins in overweight and obese women, and implications for future interventions. The following was hypothesized: walking will have a significant overall effect on serum lipid and lipoprotein profiles in overweight and obese women.

## Methodology

### Systematic Review

To develop a criteria for the search of relevant literature, the main research question (does the exclusive form of walking exercise have a significant effect on lipids and lipoproteins in overweight and obese women?) was explicated using the Participants, Interventions, Comparisons and Outcomes (PICO) question format (Higgins & Green, 2011). The following PICO question was used to complete the search of literature: will experiments of four more weeks (Pattyn, Cornelissen, Eshghi, & Vanhees, 2013) that compare at least one exclusive walking group to a control group have a significant effect on total cholesterol, triglycerides, HDLs, and LDLs in

overweight [average body mass index (BMI) between 25.0 kg/m$^2$ and 29.9 kg/m$^2$] and obese (average BMI of 30.0 kg/m$^2$ or greater) women who are ≥18 years of age? An extensive search of literature was based on this PICO question, and was systematically completed using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, Altman, & the PRISMA Group, 2009).

Academic Search Complete, Alternative Health Watch, Cumulative Index to Nursing and Allied Health Literature (CINAHL) Plus with Full Text, Global Health, Health Source - Consumer Edition, Health Source: Nursing/Academic Edition, Medical Literature Analysis and Retrieval System Online (MEDLINE), MEDLINE with full text, SportDiscus with full text, Excerpta Medica database (EMBASE), and ProQuest dissertation & theses databases were searched. Boolean logic is the search strategy that was utilized for all the databases with the following search terms: women AND lipids OR lipoproteins OR cholesterol OR triglycerides OR low-density lipoprotein OR high-density lipoprotein AND walk OR walking OR step OR steps. Following the search of databases, reference lists from fully reviewed publications were searched for additional studies not found in the search of databases. The search of literature was not restricted to the timeframe in which the studies were completed (Higgins & Green, 2011).

**Study Inclusion Criteria**

Studies were initially selected for review based on titles and abstracts from the search of databases and reference lists. Studies that met the following inclusion criteria were fully reviewed: (1) experiment-control design; (2) sample of overweight and/or obese women; (3) exclusive use of walking as the experiment's independent variable; (4) intervention period of four or more weeks; and (5) investigated changes in lipids and lipoproteins (pre- to post-experiment).

**Study Exclusion Criteria**

In order to quantify data for the meta-analyses, the selected studies had to report data for both the experiment group and control group. The reported data had to include the sample size for each group along with the test statistics (e.g., odds ratios and confidence intervals), pre- and post-events and non-events, or means and standard deviations. For studies that reported insufficient data, attempts to obtain the necessary data were made by contacting the corresponding author prior to exclusion.

**Selection of Studies**

A total of 948 studies were returned through the search of databases, and an additional nine studies were identified from the search of reference lists. Of these 957 studies, 888 were excluded after reviewing titles and abstracts. The remaining 69 studies were fully reviewed for eligibility. Upon full review of the remaining studies, 18 were excluded due to non-experiment design, 25 were excluded due to not meeting other inclusion criteria [e.g., diet plus walking or other modalities of exercise, walking plus diet counseling, walking combined with weight-training or strength conditioning (e.g., use of weight-lifting equipment), walking plus jogging, walking with use of an ergonomic aid (e.g., Nordic walking poles), minimum intervention period was not completed (e.g., one-bout or single session of walking), average BMI was less than 25 $kg/m^2$, or changes in lipids or lipoproteins were not measured]. Additionally, two studies were excluded due to duplicate data and two were excluded due to unsuccessful attempts to retrieve data from the authors, leaving 22 studies to be included in the meta-analyses. The process of selection of studies is summarized in Appendix A.

The search of databases and selection of studies were independently completed by two trained meta-analytic reviewers (Anjulyn Ballard and Ashlee Davis). After each reviewer completed the search of databases and selection of studies, the reviewers compared their lists of selections and determined if there were any differences in exclusion or inclusion of the selected studies. When there were differences, together, the Reviewers assessed the papers that were excluded/included on their opposing lists and together decided if the papers should be excluded or included in the final sample of studies.

**Data Extraction and Risk of Bias Assessment**

Baseline and post-intervention data for total cholesterol, triglycerides, LDLs, and HDLs were extracted from the selected fully reviewed studies. The sample size of the experiment and control groups, pre- and post-means, and standard deviations for the lipids and lipoproteins were extracted for the meta-analyses. For the lipids and lipoproteins, data provided in the form of millimoles per liter (mmol/L) was converted to milligrams per deciliter (mg/dL). Data extraction was independently completed by the two Reviewers. Once data extraction was independently completed, the Reviewers compared their extracted data and identified any differences. For differences that were identified, the two Reviewers assessed the articles together to confirm correct and accurate data extraction.

The two Reviewers also independently completed a risk of bias assessment on the 22 studies that remained. The risk of bias assessment was based on the following categories of bias: selection, performance, detection, attrition, and reporting. Each category was rated as high, low, or unclear risk of bias for each study. The risk of bias assessment was completed as per recommendations by the Cochrane Collaboration (Higgin et al., 2011).

## Meta-Analyses

After completion of data extraction, the meta-analyses were completed. Extracted data were entered into the Comprehensive Meta-Analysis (CMA) software (Comprehensive Meta-Analysis, version 3.0; Biostat Inc.). Separate meta-analyses were completed for total cholesterol, triglycerides, HDLs, and LDLs. A random effects model was used for the four individual meta-analyses to determine the overall raw mean difference (RMD) and significance of each lipid and lipoprotein. The random effects model was used over a fixed effects model because there was variation in experimental factors among the studies [e.g., intervention timeframe (8 weeks versus 24 weeks), aerobic intensity (moderate versus vigorous), lifecycle (pre-menopausal versus post-menopausal women)]. For each meta-analysis, each study's RMD, significance, standard error, and confidence interval were calculated.

Meta-regression analyses and sub-group analyses were completed for variables that were identified as potential moderators. The random effects model was also used to determine between-study variance (heterogeneity) for the RMD of each lipid and lipoprotein. Heterogeneity was assessed by using Q-value and $I^2$ statistics (Borenstein, Hedges, Higgins, & Rothstein, 2009). Due to the presence of heterogeneity, sub-group and meta-regression analyses were completed to identify potential moderating variables that could explain the variance that existed among each lipid and lipoprotein meta-analysis. Meta-regression analyses using the method-of-moments model were used to assess the continuous moderating variables, and sub-group analyses were used to assess the nominal moderator variables. The analyses were completed assuming a common among-study variance across the sub-groups, and only sub-group analyses with three or more studies per comparative group were completed.

## Analysis of Outcome Variables

The outcome variables were total cholesterol, triglycerides, LDLs, and HDLs. The pre- and post-means, standard deviations, and the number of subjects for the experiment and control groups were entered into the CMA software. Multiple reported outcomes (e.g., total cholesterol, triglycerides, and LDLs) from a single study were entered into the software separately and were individually calculated for their RMD and significance.

## Coding and Analysis of Moderating Variables

Moderating variables that potentially explained variance among the studies were identified. Exercise intensity, the duration in number of minutes per week, the frequency in number of days per week, the number of weeks, total walking dose, average BMI, lipid and lipoprotein baseline values, menopause stage, type of walking activity, year of study, and origin of the study (continent) are the moderating variables that were identified, coded, and entered into the CMA software.

Walking intensity was coded as low, moderate, and high as stated by the individual studies as "low," "moderate," or "high" or "vigorous" intensity. For studies that reported maximal heart rate max ($HR_{max}$), low intensity was coded for walking intensity that was less than 64% $HR_{max}$ (CDC, 2019), and low intensity was coded for studies that focused on steps per day. Moderate intensity was coded for walking intensities that were between 64% and 76% $HR_{max}$ (CDC, 2019), or for studies that indicated the walking as "brisk walking" (Piercy et al., 2018). High intensity was coded for walking intensities that were 77% or greater $HR_{max}$ (CDC, 2019). The number of minutes per week was calculated by multiplying the number of days of walking times the number of minutes per day, and coded and entered as the total number of minutes per week

(e.g., 150 minutes, 180 minutes). The number of days per week was coded and entered as the total number of days of walking per week (e.g., 3 days, 5 days). The number of weeks was coded and entered as the total number of weeks of walking (e.g., 8 weeks, 12 weeks) or when the number of months was indicated in a study, the number of months was converted to weeks (e.g., 6 months x 4 weeks per month= 24 weeks). The total walking dose was calculated and entered as the total number of walking minutes by multiplying the total number of minutes per week times the total number of weeks (e.g., 150 minutes x 16 weeks= 2,400 minutes). BMI was the average BMI of the control and experiment groups of each study and entered as the mean BMI for the individual study. Lipid (total cholesterol, triglycerides) and lipoprotein (HDLs, LDLs) baseline values were the mean baseline values of the control and experiment groups of each study and entered as the mean baseline value for the respective lipid or lipoprotein for the individual study. Menopause stage was coded and entered as pre-menopause, menopause, and post-menopause. Each stage was coded and entered for each study as explicitly identified by the authors of each study. For studies that did not explicitly identify subjects, pre-menopause was coded and entered for subjects with a mean age of less than 51 years, menopause was coded and entered for subjects with a mean age of 51 to 59 years, and post-menopause was coded and entered for subjects with a mean age of 60 or more years (CDC, 2017b). However, the majority of the studies that were coded and entered as post-menopause were explicitly identified by the study's authors as post-menopause subjects. The type of walking activity was coded and entered as self-reported, supervised, or both. The self-reported studies were studies where the experiment groups self-recorded and reported their daily or weekly activity to the assessors. The supervised studies were studies where the assessors observed or monitored the experiment groups completing weekly ac-

tivity, and the assessors recorded the activity of the subjects. The studies that were coded and entered as both are studies that used both the self-reported and the supervised method on a weekly basis, or studies that used either of the methods during a specific term of the intervention (e.g., supervised activity during the first two weeks of a six-week intervention). The year of study was coded and entered as the year the peer-reviewed study was published, or the year the dissertation was published by the institution. The continent was coded and entered as the continent of where the study was completed. The identified continents were North America, Europe, Asia, and Africa. However, upon completing the sub-group analyses, the studies that were completed in Africa had to be removed due to less than three studies that were available for the continent analyses.

The effect and significance of the number of minutes per week, the number of days per week, the number of weeks, total intervention dose, baseline values, mean BMI, mean age, and year of study were determined using meta-regression analyses; and the effect and significance of intensity, menopause stage, collection of data, and continent were determined using sub-group analyses.

**Calculation of Raw Mean Difference**

The difference in raw mean was analyzed as the effect for the meta-analyses by comparing each experiment condition to the paired control condition, along with the standard error (SE), confidence interval (CI), level of significance ($p$), and heterogeneity of RMD ($Q$-$df$, $I^2$) (Borenstein et al., 2009).

**Assessment for Publication Bias**

To assess for publication, a funnel plot for each lipid and lipoprotein meta-analysis was used to determine, based on asymmetry of the funnel, if the effect of any of the individual studies

were overestimated in the overall lipid or lipoprotein meta-analysis. The precision of the estimated intervention effect increases as the size of the study increases. As a result, effect estimates from small studies tend to scatter more widely at the bottom of the funnel plot graph. If there is bias, smaller studies that do not have statistically significant effects will create an asymmetrical appearance of the funnel plot (Higgins & Green, 2011). When asymmetry of the funnel plots was detected, the Duvall and Tweedie's trim and fill was used to assess the magnitude of impact the bias may have had (Higgins & Green, 2011).

## Results

### Sample Characteristics

The meta-analyses were comprised of 22 studies published between 1987 and 2016 that investigated changes in lipids and lipoproteins in exclusive walking interventions among overweight and obese female populations. Twenty of the studies were published in peer-reviewed articles, and two of the studies were dissertations.

The sample of 22 studies consisted of 1,206 subjects. Mean age ranged from 22 to 73 years, with a median age of 47 years. Mean BMI ranged from 25.1 $kg/m^2$ to 34.6 $kg/m^2$, with a median value of 28.4 $kg/m^2$. Change in mean BMI, from pre to post intervention, for the control groups ranged from -2.9 $kg/m^2$ to +6.9 $kg/m^2$, with a median value of +0.2 $kg/m^2$. Change in mean BMI, from pre to post intervention, for the walking groups ranged from -3.5 $kg/m^2$ to +0.31 $kg/m^2$, with a median value of -0.95 $kg/m^2$. Most of the subjects (88%) were pre- and postmenopausal women. The walking interventions ranged from eight to 104 weeks, the majority of the studies were moderate intensity ($N$=16; 72%), and 68% ($N$= 15) of the interventions were fully supervised or included supervised sessions. About half of the studies ($N$= 13; 59%) reported all the lipid and lipoprotein variables (total cholesterol, triglycerides, HDLs, LDLs). Over half of

the studies (N=15; 68%) were completed in the United States and Canada (North America), and the remaining studies were completed in Asia, Europe, and Africa. The characteristics of the sample of studies are summarized in Table 1.

Cochrane risk of bias assessment was completed on all 22 studies. The overall risk of bias for the entire sample of studies was determined to be low. For specific categories of bias, three studies were found to have high bias for selective reporting (Musto, Jacobs, Nash, DelRossi, & Perry, 2010; Verity & Ismail, 1989; & Woolf-May et al., 1999). The majority of the studies had unclear selection bias for allocation concealment (*N*= 20; 90%). However, this appeared to be due to study reporting, and not due to the methodology of the studies.

**Table 1.** Sample Characteristics

| Reference | Number of Subjects | Mean BMI | [b]△ in Mean BMI | Meno-pause Stage | Continent | Outcome Variables | | | | Number of Weeks | Intensity | [c]Total Dose (hours) | [e]Walking Activity |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | TC | TRG | HDL | LDL | | | | |
| Ahn, 2007 | 36 | 25.2 | NR | Menopause | Asia | X | X | X | X | 12 | Moderate | 30 | Supervised |
| Aldred et al., 1995 | 24 | 25.8 | -1.0 | Pre | Europe | | | | X | 12 | Moderate | 24 | Both |
| Asikainen et al., 2003 | 204 | 25.8 | -1.2 | Post | Europe | X | X | X | X | 15 | Moderate | 56.25 | Both |
| | | | | | | | | | | 24 | Low | 60 | Both |
| | | | | | | | | | | 24 | Moderate | 60 | Both |
| Buyukyazi, 2008 | 37 | 28.6 | -1.48 | Pre | Europe | X | X | X | X | 8 | Moderate and High | 26.66 | Supervised |
| Cauley et al., 1987 | 204 | 25.1 | -0.74 | Post | North America | X | X | X | | 104 | Moderate | 216.66 | Self-Reported |
| Davison & Grant, 1995 | 62 | 25.9 | -0.76 | Menopause | Europe | X | X | X | | 14 | High | 28 | Self-Reported |
| Guessogo et al., 2016 | 139 | 34.1 | -0.72 | [a]Pre and Post | Africa | X | X | X | X | 24 | Moderate | 80 | Supervised |
| Habibzadeh, 2010 | 20 | 30.5 | -1.71 | Pre | Asia | X | | | | 8 | Moderate | 12 | Supervised |
| Hinkleman & Nieman, 1993 | 36 | 28.3 | -3.5 | Pre | North America | X | X | | X | 15 | Moderate | 56.25 | Self-Reported |
| Hopewell, 1989 | 11 | 27.7 | NR | Pre | North America | X | X | X | X | 12 | Moderate | 25 | Supervised |
| | | | | | | | | | | 24 | Moderate | 40 | Supervised |
| Keller & Trevino, 2001 | 36 | 34.6 | 0 | Pre | North America | X | X | X | X | 24 | Moderate | [d]36-60 | Self-Reported |
| Kim, 2004 | 29 | 30.4 | +0.31 | Pre | Asia | X | X | X | | 12 | Moderate | 24 | Supervised |
| Mezghanni et al., 2012 | 20 | 33.6 | -3.1 | Pre | Africa | X | X | X | X | 12 | Moderate | 45 | Supervised |
| Miller, 1995 | 37 | 25.1 | -0.95 | Pre | North America | X | X | X | X | 14 | Moderate | [d]35-70 | Supervised |
| Musto et al., 2010 | 77 | 30.1 | -0.7 | Pre | North America | | X | X | | 12 | Low | 30 | Self-Reported |
| Nieman et al., 1993 | 30 | 26.0 | +0.3 | Post | North America | X | X | X | X | 5 | Moderate | 14.58 | Supervised |
| | | | | | | | | | | 12 | Moderate | 35 | Supervised |
| Nieman et al., 2002 | 43 | 32 | -1.0 | Pre | North America | X | X | X | X | 12 | High | 45 | Supervised |
| Ready et al., 1995 | 25 | 30.7 | -1.9 | Post | North America | X | X | X | X | 24 | Moderate | 120 | Both |
| Ready et al., 1996 | 53 | 26.5 | -0.3 | Post | North America | X | X | X | X | 24 | Moderate | [d]72-120 | Both |
| Seals et al., 2001 | 35 | 28.5 | -0.1 | Post | North America | X | X | X | X | 13 | High | 43.33 | Self-Reported |
| Verity and Ismail, 1989 | 10 | 30.3 | -2.1 | Post | North America | X | | X | | 16 | High | 48 | Supervised |
| Woolf-May et al., 1999 | 38 | 26.2 | NR | Menopause | Europe | X | | X | | 18 | High | [d]44.70-47.40 | Self-Reported |

[a]Groups of both; [b]Change in mean BMI (kg/m$^2$) of the walking groups; [c]Total Dose= total intervention minutes converted total number of hours (total minutes per week x total number of weeks); [d]Multiple groups; [e]Self-reported activity was self-recorded and reported by the walking groups, and supervised activity was walking activity monitored by research assessors; NR= Not reported; TC= Total Cholesterol, TG= Triglycerides, HDL= High-Density Lipoproteins, LDL= Low-Density Lipoproteins.

**Baseline Characteristics of Lipids and Lipoproteins**

The mean for total cholesterol ranged from 177.88 mg/dL to 258.70 mg/dL, with a median value of 206.06 mg/dL. The median value for total cholesterol was borderline abnormal (> 200 mg/dL; CDC, 2015). The mean for triglycerides ranged from 82.38 mg/dL to 176.26 mg/dL, with a median value of 116.01 mg/dL. The median value for triglycerides was normal (<150 mg/dL; CDC, 2015). The mean for high-density lipoproteins ranged from 40.61 mg/dL to 64.97 mg/dL, with a median value of 54.05 mg/dL. The median value for HDLs was borderline abnormal (<60 mg/dL; CDC, 2015). The mean for low-density lipoproteins ranged from 110.00 mg/dL to 181.63 mg/dL, with a median value of 125.91 mg/dL. The median value for LDLs was abnormal (> 100 mg/dL; CDC, 2015) (Table 2).

**Table 2.** Baseline Lipids and Lipoproteins

| | | Sample Mean | | | |
|---|---|---|---|---|---|
| Outcome Variable | *n* | Minimum (mg/dL) | Maximum (mg/dL) | Median Value (mg/dL) | Status |
| Total Cholesterol | 20 | 177.88 | 258.70 | 206.06 | Abnormal |
| Triglycerides | 18 | 82.38 | 176.26 | 116.01 | Normal |
| High-Density Lipoproteins | 19 | 40.61 | 64.97 | 54.05 | Abnormal |
| Low-Density Lipoproteins | 15 | 110.00 | 181.63 | 125.91 | Abnormal |

mg/dL= milligrams per deciliter

**Meta-Analyses for Total Cholesterol**

Twenty of the 22 studies assessed pre- to post-changes in total cholesterol. The RMD between the control and experiment groups ranged from -21.95 mg/dL to +50.0 mg/dL (Table 3). The first six studies in Figure 1 resulted in negative RMDs, meaning the control groups exhibited better results than the walking groups in those studies. Conversely, 14 of the 20 studies resulted in positive RMDs, which means the walking groups demonstrated better results than the control groups in these studies. Meta-analysis of the 20 studies yielded an overall positive RMD for total cholesterol (overall RMD= +6.67 mg/dL, $p$= .04; *SE*= 3.19; 95% *CI:* +0.42 to +12.92) (Table 3). The positive RMD indicates that the walkers had a greater decrease in total cholesterol values than the control groups. The study by Guessogo et al. (2016) had the greatest influence on the overall RMD. If the Guessogo et al. (2016) study was removed from the analysis, the overall RMD would be even smaller and not statistically significant (overall RMD= +2.45, 95% CI -0.61 to +5.50; $p$= .12).

**Table 3.** Summary of Overall Results of Meta-Analyses

| Outcome Variable | *n* | RMD Range (mg/dL) | Overall RMD (mg/dL) | Overall Standard Error | Overall Confidence Interval | *p* value |
|---|---|---|---|---|---|---|
| Total Cholesterol | 20 | -21.95 to +50.0 | +6.67 | 3.19 | +0.42, +12.91 | 0.04 |
| Triglycerides | 18 | -16.9 to +45.0 | +2.82 | 5.02 | -7.03, +12.67 | 0.57 |
| High-Density Lipoproteins | 19 | -4.41 to +15.0 | +1.27 | .86 | -0.42, +2.95 | 0.14 |
| Low-Density Lipoproteins | 15 | -5.95 to +40.0 | +7.38 | 3.64 | .26, +14.51 | 0.04 |

RMD= raw mean difference; mg/dL= milligrams per deciliter

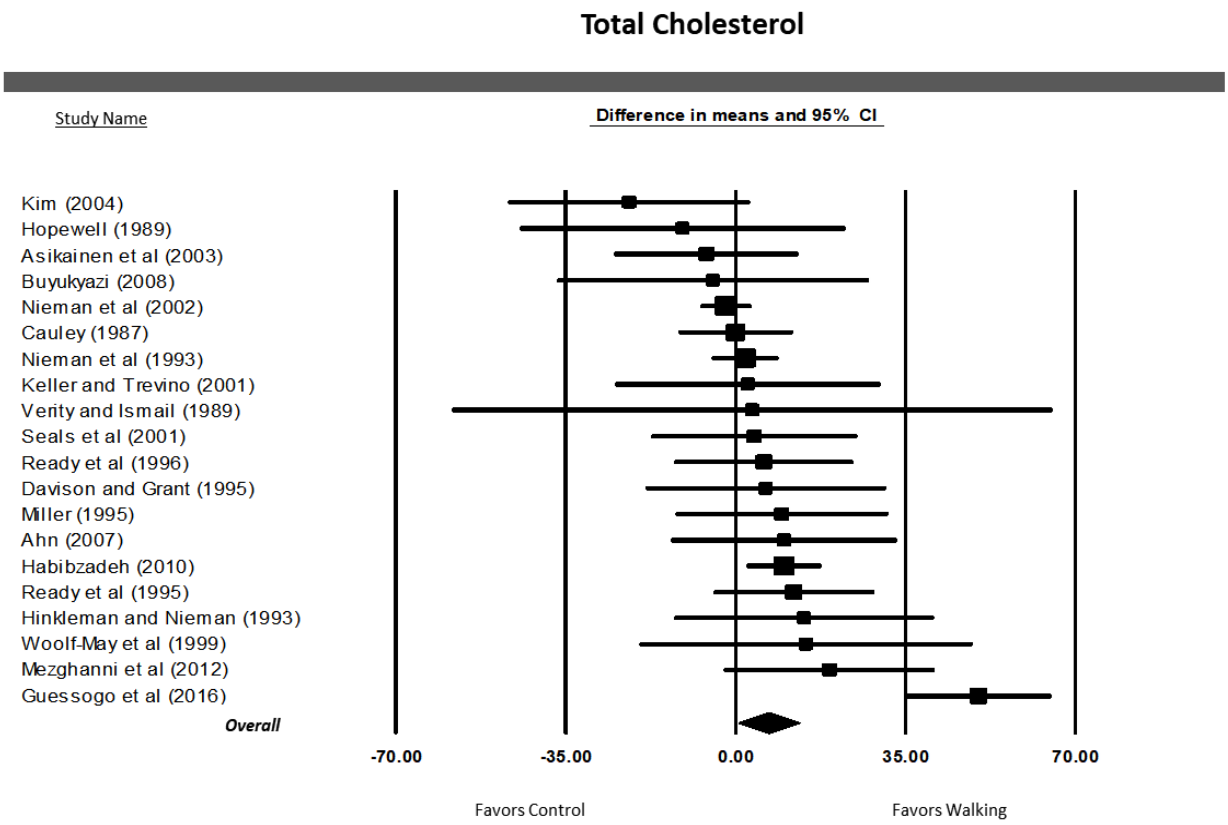


**Figure 1.** Forest plot of raw mean differences (RMDs) from the 20 studies that assessed the effect of walking on total cholesterol. A square in the plot represents the RMD for a given study with the size of the square being proportional to the weighting of that study in the meta-analysis. The horizontal line is the 95% confidence interval (CI) for the study's RMD. Studies are arranged from the lowest to highest RMD. The diamond at the bottom represents the overall RMD calculated using a random-effects model. The width of the diamond represents the 95% CI for the overall RMD.

Publication bias appeared to affect the overall RMD. There was asymmetry in the funnel plot of RMDs for total cholesterol versus standard error (Appendix B). The Duval and Tweedie's trim and fill adjustment was applied to correct for potential publication bias, and the overall RMD changed from +6.67 mg/dL to +2.31 mg/dL. The asymmetry in the funnel plot seemed to primarily result from the Verity & Ismail (1989) study. The trim and fill adjustment resulted in a smaller RMD between the experiment and control groups (overall RMD= +2.31 mg/dL).

Assessment of heterogeneity of the studies resulted in variance that was moderate ($I^2$= 64%), and statistically significant ($Q$-$df$= 54.04, $p$< 0.01). Due to moderate between-study variance, subgroup and meta-regression analyses were completed to determine if the potential moderator variables explain some the variance. In the sub-group analyses, there was no significant difference in RMD between moderate and high intensity walking ($p$= 0.81) (low intensity was removed due to less than three studies for the analysis) (Table 4). Also, there was no significant difference in RMD between pre-menopause, menopause, and post-menopause women ($p$= 0.98). There was no significant difference between self-reported studies, supervised studies, and studies that used a combination of both types of walking activities ($p$= 0.81). There was no significant difference between the Asian, European and North American studies ($p$= 0.25) (Table 4). Meta-regression analyses for mean BMI ($p$= 0.02) (Figure 2) and year of study ($p$= 0.02) (Figure 3) were significant. However, the meta-regression analyses for total walking dose ($p$= 0.42), minutes per week ($p$= 0.23), number of days per week ($p$= 0.80), number of weeks ($p$= 0.92), and the baseline triglyceride values ($p$= 0.37) were not significant.

**Table 4.** Summary of Subgroup Analyses Examining Nominal Moderator Variables That May Explain Between-Study Variance in Raw Mean Difference for Total Cholesterol

| Moderator Variable | Comparison | | | *p* value |
|---|---|---|---|---|
| | *n* | RMD | *CI* | |
| Intensity | | | | 0.81 |
| Moderate | 16 | +5.33 | -2.51, +13.18 | |
| High | 6 | +3.32 | -11.27, +17.92 | |
| Menopause Stage | | | | 0.98 |
| Pre-Menopause | 10 | +8.29 | -3.43, +20.01 | |
| Menopause | 3 | +9.40 | -5.80, +24.62 | |
| Post-Menopause | 8 | +9.86 | -3.44, +22.56 | |
| Type of Walking Activity | | | | 0.81 |
| Self-Reported | 6 | +3.67 | -4.59, +11.94 | |
| Supervised | 11 | +7.75 | -2. 02, +17.54 | |
| Both | 3 | +4.70 | -5.64, +15.06 | |
| Continent | | | | 0.25 |
| North America | 11 | +0.90 | -2.65, +4.46 | |
| Europe | 4 | +0.18 | -12.50, +12.88 | |
| Asia | 3 | +7.42 | +0.35, +14.48 | |

RMD= raw mean difference; CI= confidence interval

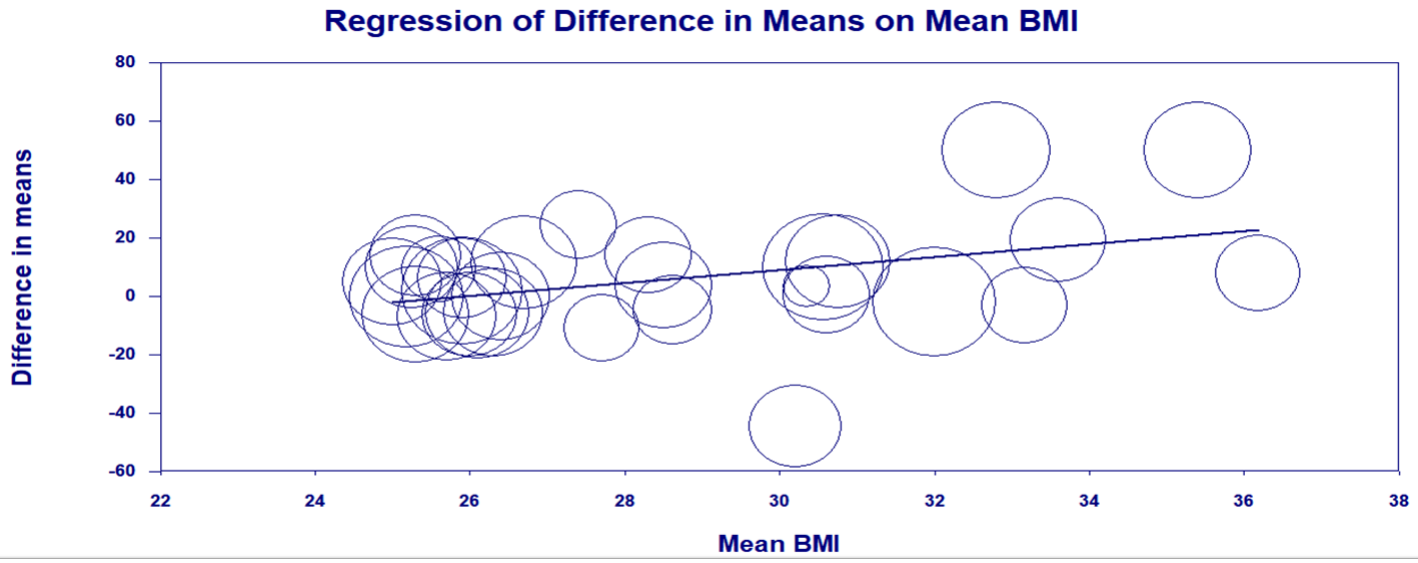


**Figure 2.** Scatterplot of meta-regression of difference in means on mean BMI for total cholesterol.

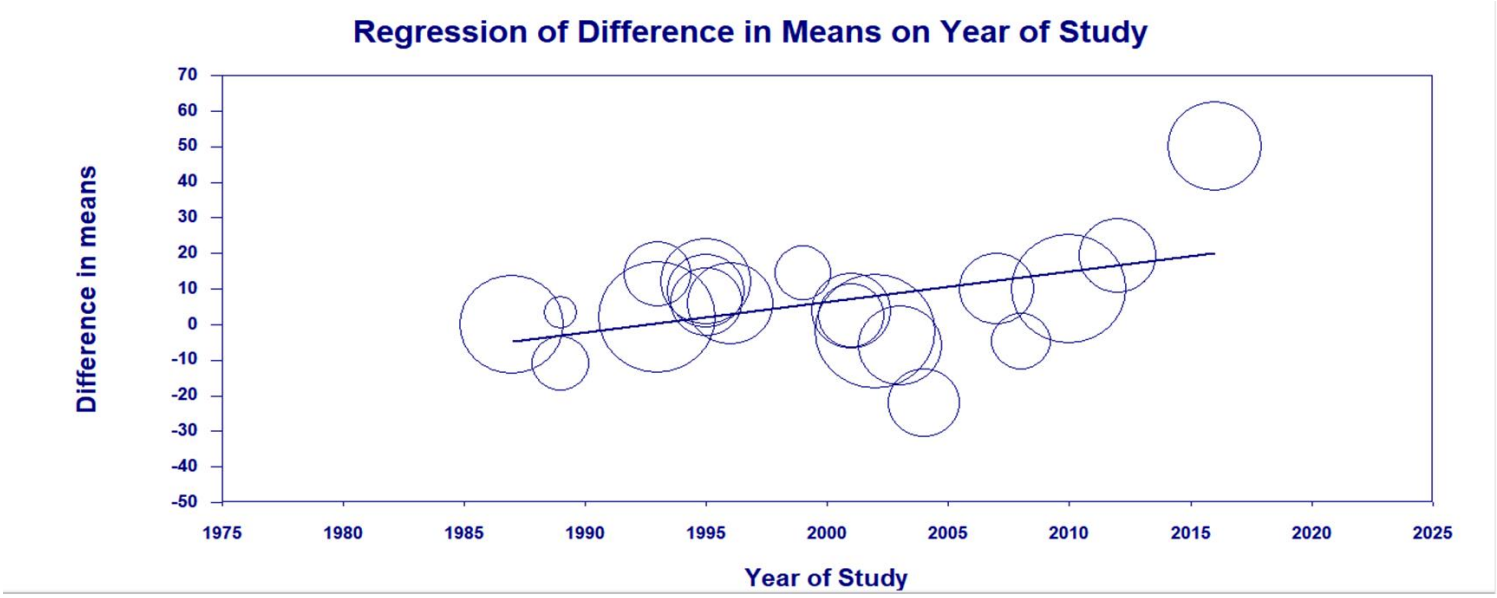


**Figure 3.** Scatterplot of meta-regression of difference in means on year of study for total cholesterol.

**Meta-Analyses for Triglycerides**

Eighteen of the 22 studies assessed pre- to post-changes in triglycerides. The RMD between the control and experiment groups ranged from -16.9 mg/dL to +45.0 mg/dL (Table 3). The first 11 studies in Figure 4 resulted in negative RMDs, meaning the control groups exhibited better results than the walking groups in those studies. Conversely, seven of the 18 studies resulted in positive RMDs, which indicates the walking groups demonstrated better results than the control groups in those studies. Meta-analysis of the 18 studies yielded an overall positive RMD for triglycerides (overall RMD= +2.82 mg/dL, $p$= 0.57; *SE*=5.02; 95% *CI:* -7.03 to +12.67) (Table 3). However, although the positive RMD indicates that the walkers had a greater decrease in triglyceride values than the control groups, the overall change was small and not statistically significant. No single study dominated the calculation of the overall RMD. The study by Nieman et al. (1993) had the largest effect on the overall RMD, but if it was removed from the analysis, the overall RMD would still be small and not statistically significant (overall RMD= +5.12, 95% CI -4.51 to +14.76; $p$= 0.30).

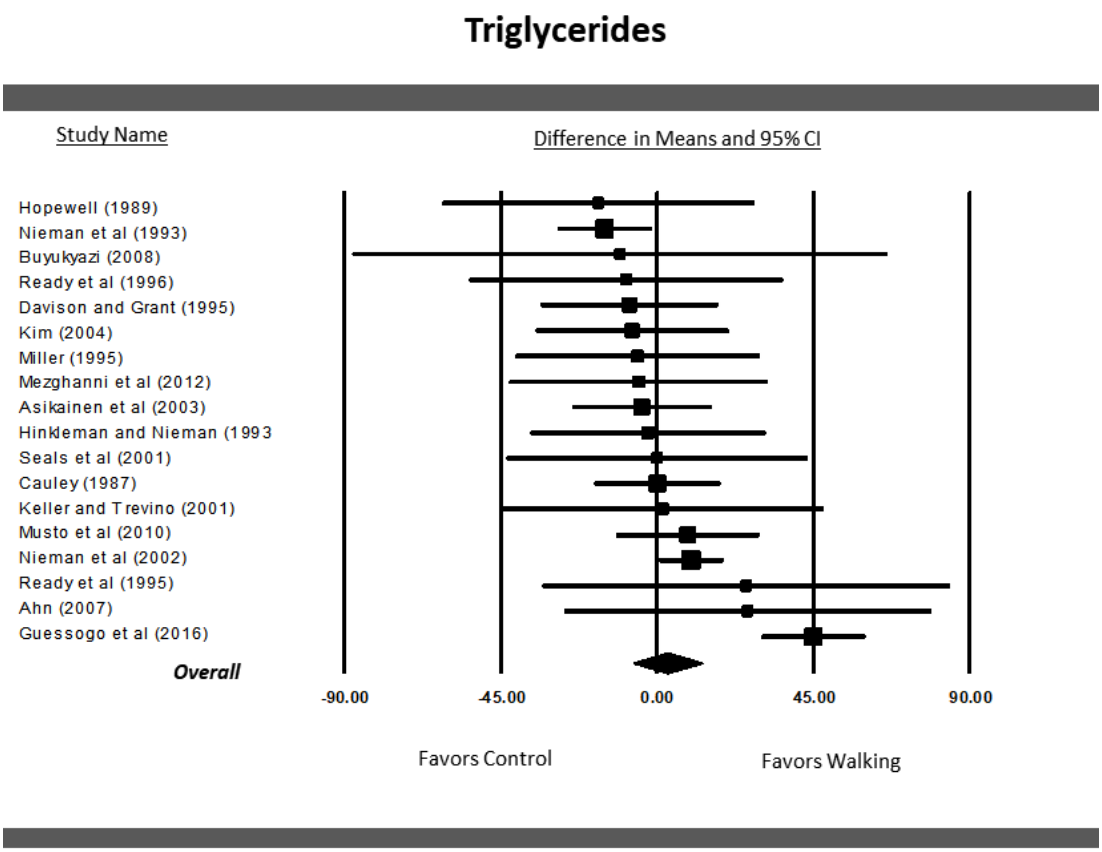


**Figure 4.** Forest plot of raw mean differences (RMDs) from the 18 studies that assessed the effect of walking on triglycerides. A square in the plot represents the RMD for a given study with the size of the square being proportional to the weighting of that study in the meta-analysis. The horizontal line is the 95% confidence interval (CI) for the study's RMD. Studies are arranged from the lowest to highest RMD. The diamond at the bottom represents the overall RMD calculated using a random-effects model. The width of the diamond represents the 95% CI for the overall RMD.

Publication bias did not appear to affect the overall RMD. There was minor asymmetry in the funnel plot of RMDs for triglycerides versus standard error (Appendix C). The Duval and Tweedie's trim and fill adjustment was applied to correct for potential publication bias, but the overall RMD did not change (overall RMD= +2.82 mg/dL).

Assessment of heterogeneity of the studies indicated that variance was moderate ($I^2$= 60%), and statistically significant ($Q$-$df$= 43.17, $p$< 0.01). Due to moderate between-study variance, subgroup and meta-regression analyses were completed to determine if the potential moderator variables explain some the variance. In the sub-group analyses, there was no significant difference in RMD between low, moderate, and high intensity walking ($p$= 0.99) (Table 5). Also, there was no significant difference in RMD between pre-menopause and post-menopause women ($p$= 0.91) (menopause stage was not included due to less than three studies for the analysis). There was not a significant difference between self-reported studies, supervised studies, and the studies that used a combination of both methods ($p$= 0.89). There was no significant difference between the European and North American countries ($p$= 0.38) (Asia was not included due to less than three studies for the analysis) (Table 5). Meta-regression analyses for mean BMI ($p$< 0.01) (Figure 5) and year of study ($p$< 0.01) (Figure 6) were significant. However, the meta-regression analyses for total walking dose ($p$= 0.34), minutes per week ($p$= 0.45), number of days per week ($p$= 0.51), number of weeks ($p$= 0.67), and the baseline triglyceride values ($p$= 0.50) were not significant.

**Table 5.** Summary of Subgroup Analyses Examining Nominal Moderator Variables That May Explain Between-Study Variance in Raw Mean Difference for Triglycerides

| Moderator Variable | Comparison | | | *p* value |
|---|---|---|---|---|
| | *n* | RMD | *CI* | |
| Intensity | | | | 0.99 |
| Low | 3 | +0.42 | -20.18, +21.03 | |
| Moderate | 16 | +1.04 | -9.54, +11.63 | |
| High | 4 | +1.17 | -20.29, +22.64 | |
| Menopause Stage | | | | 0.91 |
| Pre-Menopause | 10 | +6.29 | -10.14, +22.72 | |
| Post-Menopause | 7 | +4.90 | -13.89, +23.69 | |
| Type of Walking Activity | | | | 0.89 |
| Self-Reported | 6 | +0.24 | -17.47, +17.96 | |
| Supervised | 9 | +5.06 | -9.44, +19.56 | |
| Both | 3 | -0.21 | -28.31, +27.88 | |
| Continent | | | | 0.38 |
| North America | 11 | +1.49 | -4.67, +7.65 | |
| Europe | 3 | -5.96 | -21.46, +9.53 | |

RMD= raw mean difference; CI= confidence interval

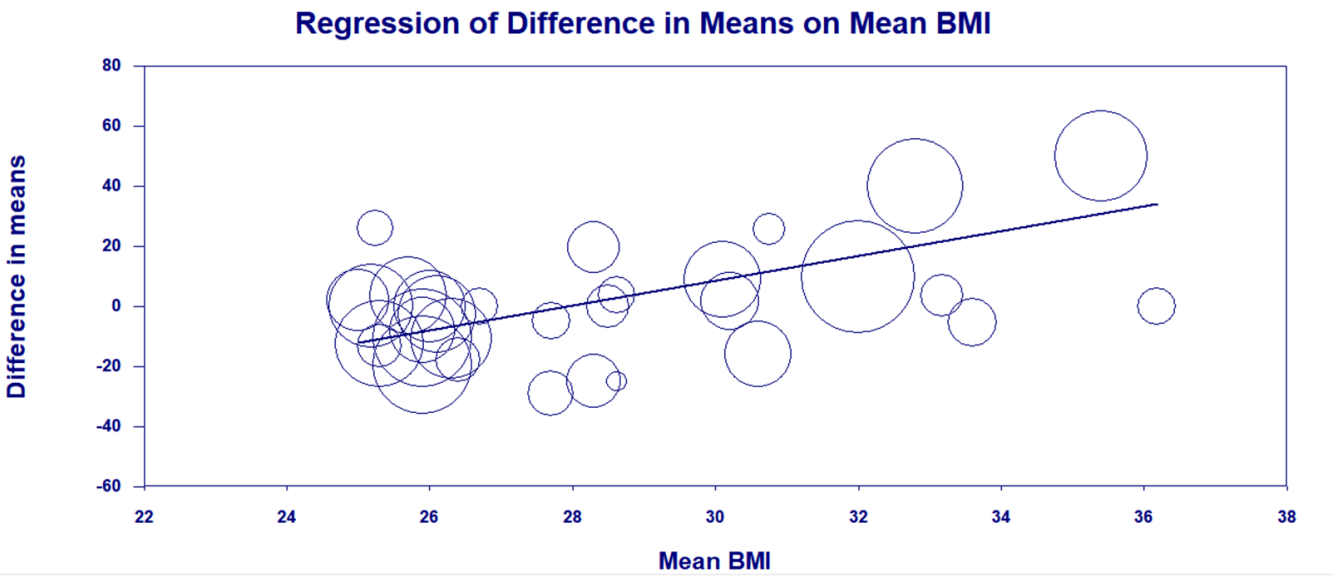


**Figure 5.** Scatterplot of meta-regression of difference in means on mean BMI for triglycerides.

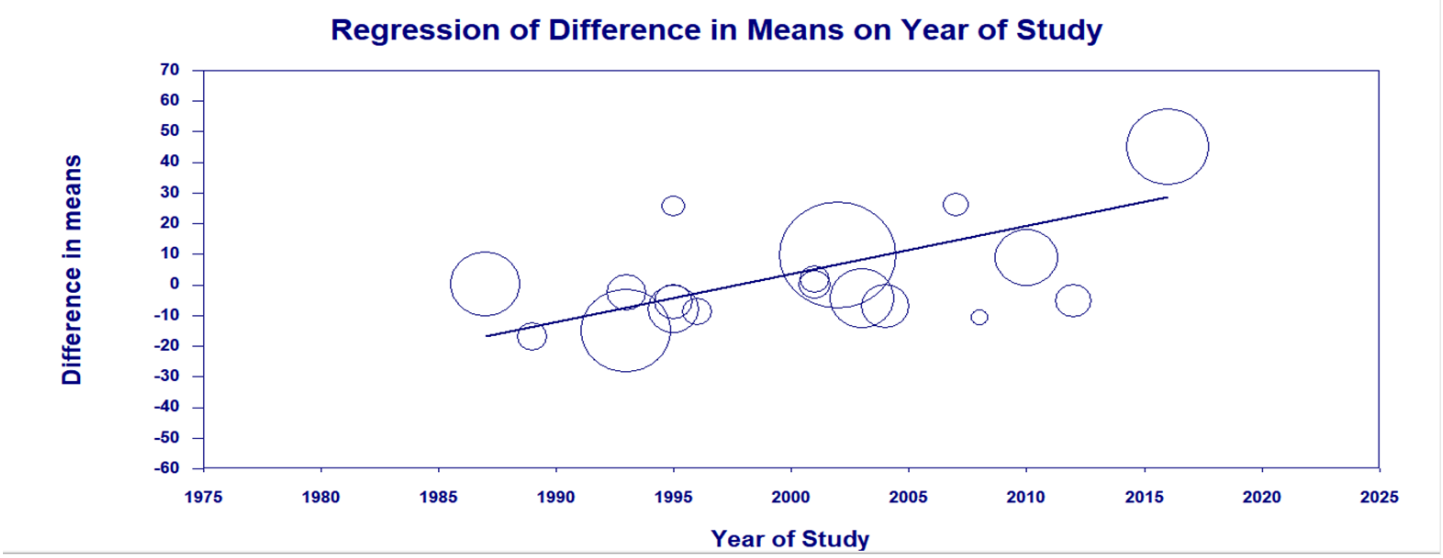


**Figure 6.** Scatterplot of meta-regression of difference in means on year of study for triglycerides.

**Meta-Analyses for HDLs**

Nineteen of the 22 studies assessed pre- to post-changes in HDLs. The RMD between the control and experiment groups ranged from -4.41 mg/dL to +15.0 mg/dL (Table 3). The first five studies in Figure 7 resulted in negative RMDs, meaning the control groups exhibited better results than the walking groups in those studies. Conversely, 12 of the 19 studies resulted in positive RMDs, which means the walking groups demonstrated better results than the control groups; and two studies exhibited no RMD in HDLs between the experiment and control groups. Meta-analysis of the 19 studies yielded an overall positive RMD for HDLs (overall RMD= +1.27 mg/dL, $p$= 0.14; *SE*= 0.86; 95% *CI:* -0.42 to +2.95) (Table 3). While the positive RMD indicates that the walkers had a greater increase in HDL values than the control groups, the overall change was small and not statistically significant. No single study dominated the calculation of the overall RMD. The study by Nieman et al. (2002) had the largest effect on the overall RMD, but if it was removed from the analysis, the overall RMD would be small and not statistically significant (overall RMD= +1.74, 95% CI -0.27 to +3.76; $p$= 0.09).

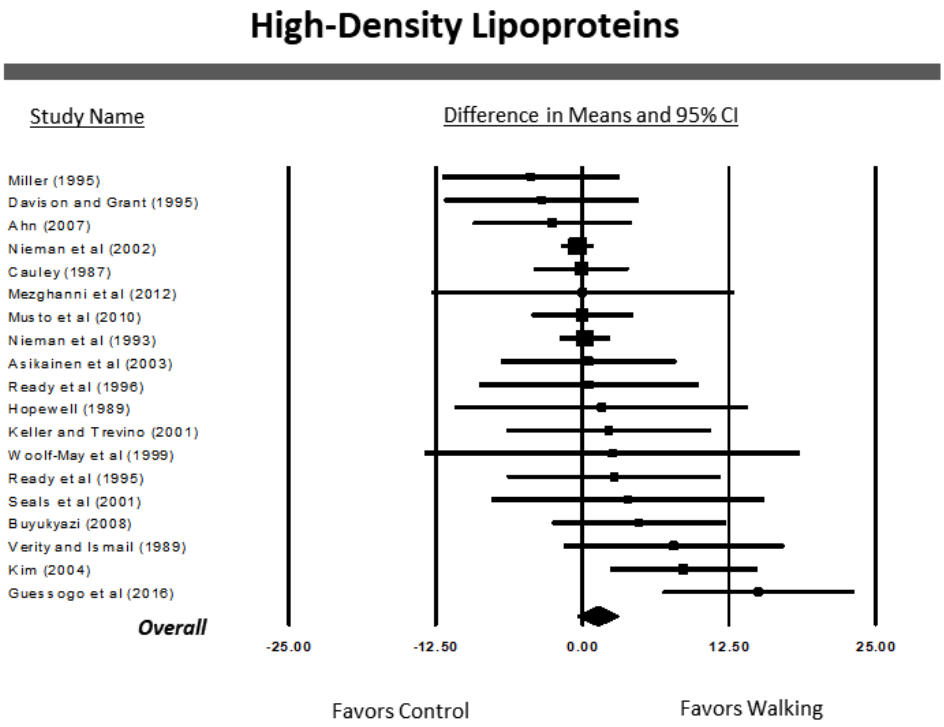


**Figure 7.** Forest plot of raw mean differences (RMDs) from the 19 studies that assessed the effect of walking on HDLs. A square in the plot represents the RMD for a given study with the size of the square being proportional to the weighting of that study in the meta-analysis. The horizontal line is the 95% confidence interval (CI) for the study's RMD. Studies are arranged from the lowest to highest RMD. The diamond at the bottom represents the overall RMD calculated using a random-effects model. The width of the diamond represents the 95% CI for the overall RMD.

Publication bias appeared to affect the overall RMD. There was asymmetry in the funnel plot of RMDs for HDLs versus standard error (Appendix D). The Duval and Tweedie's trim and fill adjustment was applied to correct for potential publication bias, and the overall RMD changed from +1.27 mg/dL to -0.37 mg/dL. The asymmetry in the funnel plot seemed to result from the Buyukyazi (2008) and Seals et al. (2001) studies. The trim and fill adjustment resulted in a smaller RMD between the experiment and control groups (overall RMD= -0.37 mg/dL).

Between study variance (heterogeneity) of the studies was small ($I^2$= 35%), and not statistically significant ($Q$-$df$= 28.0, $p$= 0.06). Subgroup and meta-regression analyses were completed to determine if the potential moderator variables explain the minor variance that existed. In the sub-group analyses, there was no significant difference in RMD between moderate and high intensity walking ($p$= 0.77) (low intensity studies were removed due to less than three studies for the analysis) (Table 6). There was no significant difference in RMD between pre-menopause, menopause, and post-menopause women ($p$= 0.32). There was no significant difference between self-reported studies, supervised studies, and the studies that used a combination of both methods ($p$= 0.68). There was no significant difference between the European and North American studies ($p$= 0.62) (Asia was not included due to less than three studies for the analysis) (Table 6). Meta-regression analyses for mean BMI ($p$< 0.01) (Figure 8) and the number of days per week ($p$= 0.02) (Figure 9) were significant. However, the meta-regression analyses for year of study ($p$= 0.14), total walking dose ($p$= 0.95), minute per week ($p$= 0.62), number of weeks ($p$= 0.92), and the baseline HDL values ($p$= 0.79) were not significant.

**Table 6.** Summary of Subgroup Analyses Examining Nominal Moderator Variables That May Explain Between-Study Variance in Raw Mean Difference for High-Density Lipoproteins

| Moderator Variable | Comparison | | | *p* value |
|---|---|---|---|---|
| | *n* | RMD | *CI* | |
| Intensity | | | | 0.77 |
| Moderate | 13 | +1.95 | -.45, +4.35 | |
| High | 6 | +1.32 | -2.25, +4.91 | |
| Menopause Stage | | | | 0.32 |
| Pre-Menopause | 9 | +2.25 | -1.14, +5.64 | |
| Menopause | 3 | -2.14 | -8.93, +4.64 | |
| Post-Menopause | 8 | +3.74 | +0.14, +7.33 | |
| Type of Walking Activity | | | | 0.68 |
| Self-Reported | 6 | +0.18 | -3.20, +3.57 | |
| Supervised | 10 | +2.00 | -0.34, +4.35 | |
| Both | 3 | +1.20 | -4.33, +6.75 | |
| Continent | | | | 0.62 |
| North America | 11 | -0.04 | -1.08, +1.00 | |
| Europe | 4 | +1.04 | -3.23, +5.32 | |

RMD= raw mean difference; CI= confidence interval

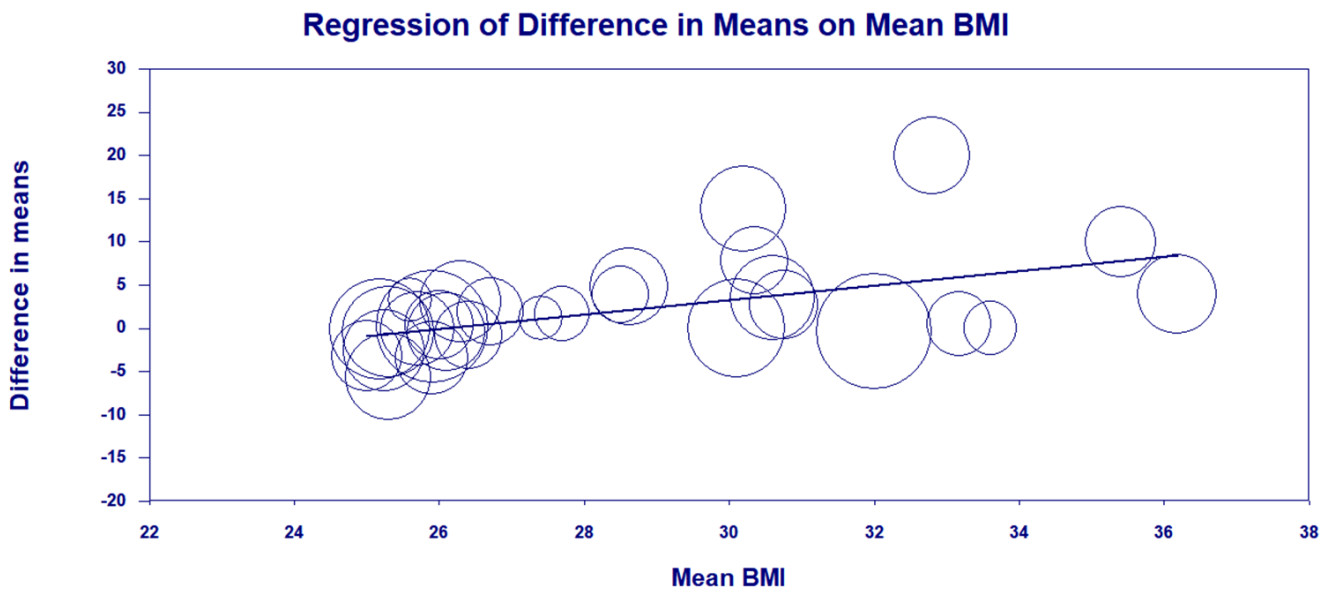


**Figure 8.** Scatterplot of meta-regression of difference in means on mean BMI for high-density lipoproteins.

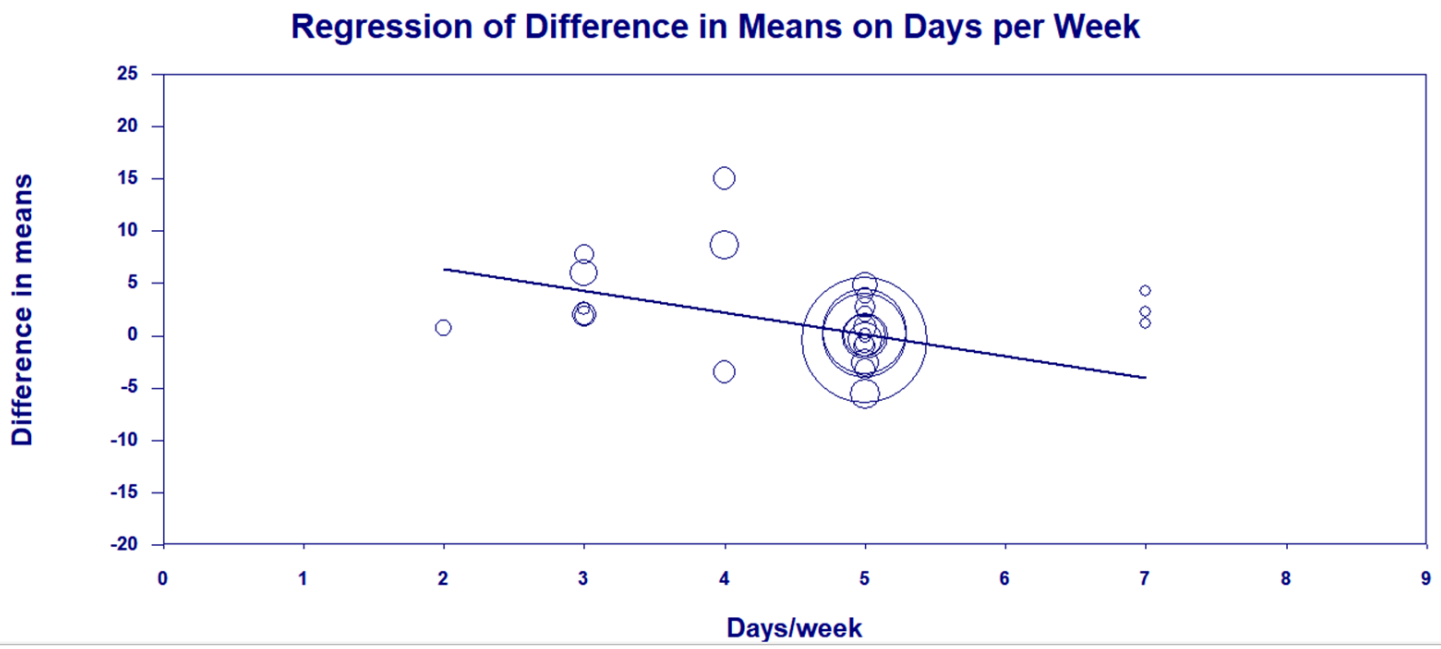


**Figure 9.** Scatterplot of meta-regression of difference in means on days per week for high-density lipoproteins.

**Meta-Analyses for LDLs**

Fifteen of the 22 studies assessed pre- to post-changes in LDLs. The RMD between the control and experiment groups ranged from -5.95 mg/dL to +40.0 mg/dL (Table 3). The first three studies in Figure 10 resulted in negative RMDs, meaning the control groups exhibited better results than the walking groups in those studies. Conversely, 11 of the 15 studies resulted in positive RMDs, which indicates that the walking groups demonstrated better results than the control groups in these studies; and one study exhibited no RMD in LDLs between the experiment and control groups. Meta-analysis of the 15 studies yielded an overall positive RMD for LDLs (overall RMD= +7.38 mg/dL, $p$= 0.04; $SE$= 3.64; 95% *CI:* +0.26 to +14.51) (Table 3). The positive RMD indicates that the walkers had a greater decrease in LDL values than the control groups. However, the study by Guessogo et al. (2016) had the greatest influence on the overall RMD. If the Guessogo et al. (2016) study was removed from the analysis, the overall RMD would be even smaller and not statistically significant (overall RMD= +3.81, 95% CI -0.73 to +8.36; $p$= 0.10).

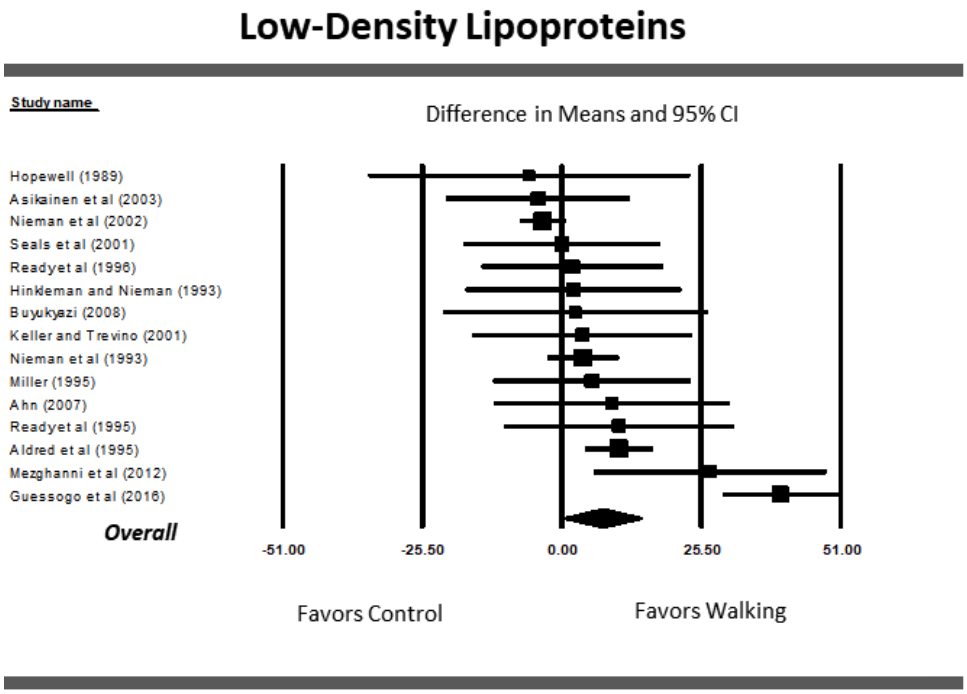


**Figure 10.** Forest plot of raw mean differences (RMDs) from the 15 studies that assessed the effect of walking on LDLs. A square in the plot represents the RMD for a given study with the size of the square being proportional to the weighting of that study in the meta-analysis. The horizontal line is the 95% confidence interval (CI) for the study's RMD. Studies are arranged from the lowest to highest RMD. The diamond at the bottom represents the overall RMD calculated using a random-effects model. The width of the diamond represents the 95% CI for the overall RMD.

Publication bias did not appear to affect the overall RMD. There was very minor asymmetry in the funnel plot of RMDs for LDLs versus standard error (Appendix E). The Duval and Tweedie's trim and fill adjustment was applied to correct for potential publication bias, but the overall RMD did not change (overall RMD= +7.38 mg/dL).

Between study variance of the studies was large ($I^2$= 79%), and statistically significant ($Q$-$df$= 67.8, $p$< 0.01). Subgroup and meta-regression analyses were completed to determine if the potential moderator variables explain the variance. In the sub-group analyses, there was no significant difference in RMD between moderate and high intensity walking ($p$= 0.35) (low intensity was not included due to less than three studies for the analysis) (Table 7). There was no significant difference in RMD between pre-menopause and post-menopause women (p= 0.78) (menopause was not included due to less than three studies for the analysis). There was no significant difference between self-reported studies, supervised studies, and the studies that used a combination of both methods ($p$= 0.68). However, there was a significant RMD between the European and North American studies ($p$= 0.01) (Asia was not included due to less than three studies for the analysis) (Table 7). Meta-regression analyses for mean BMI ($p$= 0.03) (Figure 11), and year of study ($p$= 0.02) (Figure 12) were significant. However, the meta-regression analyses for total walking dose ($p$= 0.65), minute per week ($p$= 0.99), number of days per week ($p$= 0.81), number of weeks ($p$= 0.54), and the baseline LDL values ($p$= 0.80) were not significant.

**Table 7.** Summary of Subgroup Analyses Examining Nominal Moderator Variables That May Explain Between-Study Variance in Raw Mean Difference for Low-Density Lipoproteins

| Moderator Variable | Comparison | | | *p* value |
|---|---|---|---|---|
| | *n* | RMD | *CI* | |
| Intensity | | | | 0.35 |
| Moderate | 13 | +8.57 | +1.09, +16.06 | |
| High | 3 | +0.52 | -14.62, +15.67 | |
| Menopause Stage | | | | 0.78 |
| Pre-Menopause | 9 | +8.56 | -3.38, +20.51 | |
| Post-Menopause | 6 | +11.13 | -3.06, +25.34 | |
| Type of Walking Activity | | | | 0.68 |
| Self-Reported | 3 | +1.90 | -16.60, +20.42 | |
| Supervised | 8 | +10.44 | -0.40, +21.30 | |
| Both | 4 | +4.90 | -10.02, +19.83 | |
| Continent | | | | |
| North America | 9 | -0.54 | -3.72, +2.64 | 0.01 |
| Europe | 4 | +7.71 | +2.25, +13.18 | |

RMD= raw mean difference; CI= confidence interval

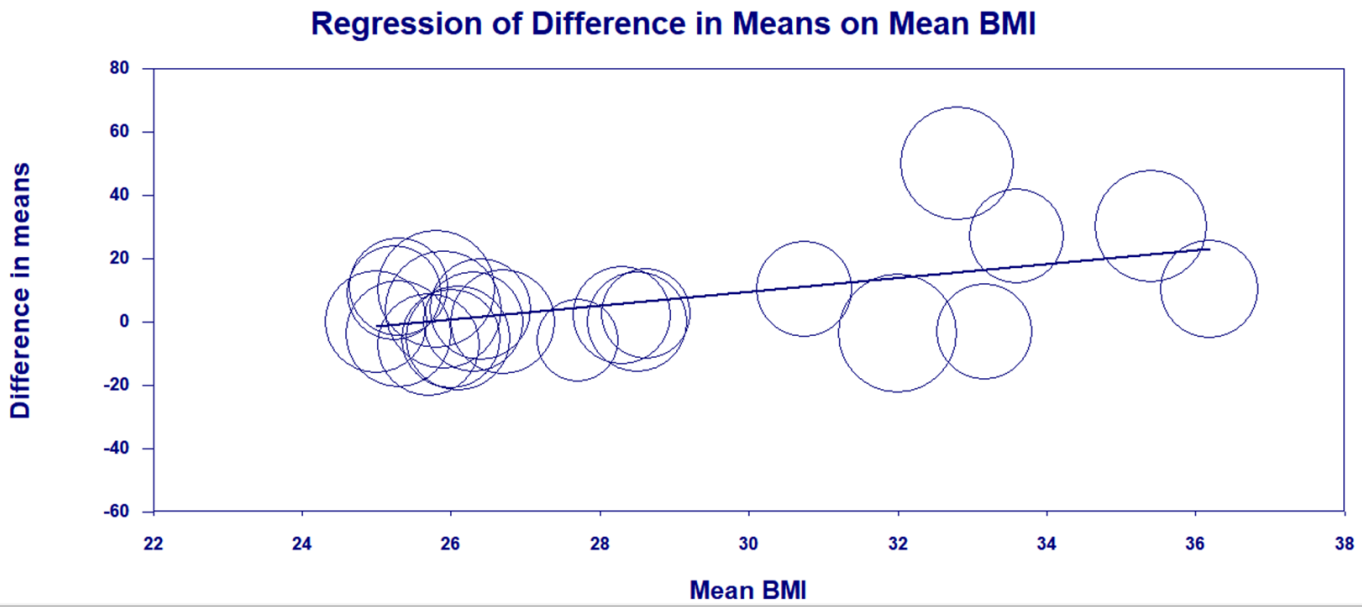


**Figure 11.** Scatterplot of meta-regression of difference in means on mean BMI for low-density lipoproteins.

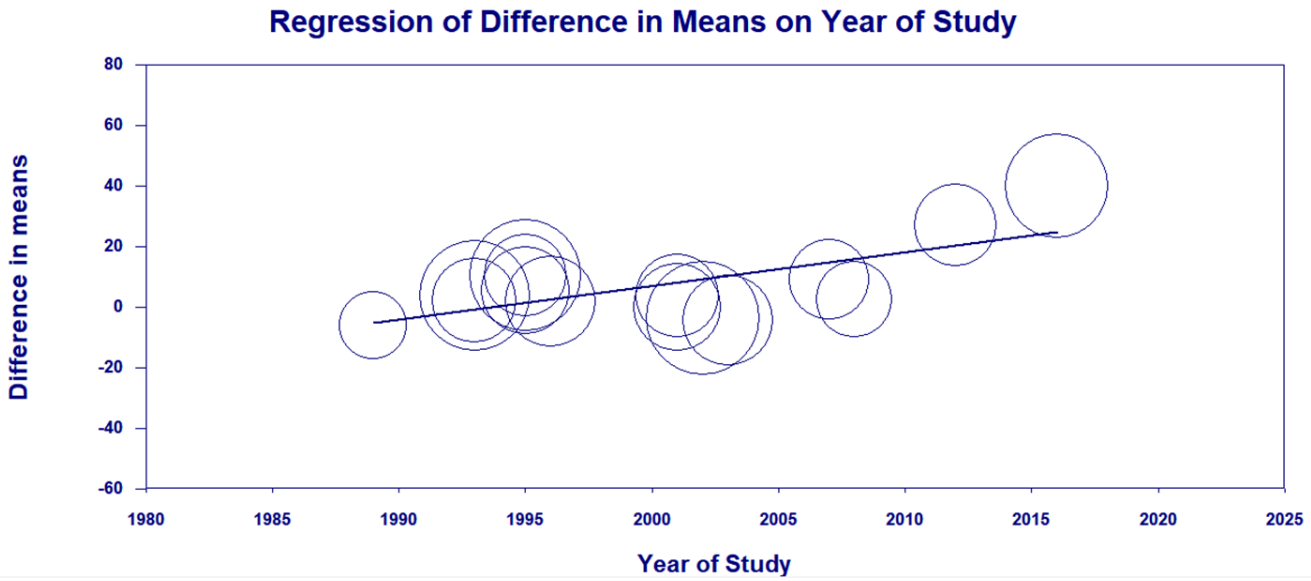


**Figure 12.** Scatterplot of meta-regression of difference in means on year of study for low-density lipoproteins.

## Discussion

The purpose of this study was to determine if exclusive walking significantly improved total cholesterol, triglycerides, HDLs, and LDLs in overweight and obese women. Similar meta-analyses that included general populations, have found significant improvement in total cholesterol (Hanson & Jones, 2015), and LDLs (Kelley, G. A., Kelley, K. S., & Tran, 2004). In this meta-analysis, total cholesterol and LDLs were the lipid and lipoprotein that resulted in significant improvement. Therefore, the hypothesis was partially supported as the improvements in triglycerides and HDLs were not statistically significant. Consistent with Hanson and Jones (2015), total cholesterol significantly improved, and the significant improvement in LDLs was consistent with the Kelly et al. (2004) meta-analysis. In addition, this meta-analysis and the previous meta-analyses (Hanson & Jones, 2015; Kelley, et al. 2004) demonstrated no significant improvement in triglycerides and HDLs. Unlike the previous meta-analyses, this meta-analysis calculated the effects of walking on the outcome variables in an exclusive overweight and obese population. Surprisingly, HDLs were not significantly improved, but previous studies that used moderate-intensity aerobic activity for overweight and obese women have demonstrated significant improvement (Cao, Jiang, Li, Wang, & Tan, 2019; Vatansev & Cakmakci, 2010). A previous review of literature summarized that a dose-response relationship exists, where a higher level of HDLs is related to more expended energy (Hardman, 1999). It is possible that significant improvement of HDLs occurs under moderate to vigorous-intensity aerobic activity, or under prolonged aerobic activity that exists for several weeks or months for overweight and obese individuals (Hardman, 1999). However, future interventions that investigate the effects of aerobic activity on HDLs in obese population should be supervised. For example, the Cao et al. (2019) and

Vatansev & Cakmakci (2010) studies were supervised interventions where the prescribed intensities were maintained during the aerobic sessions. However, this meta-analysis and the previous meta-analyses (Hanson & Jones, 2015; Kelley, et al. 2004) were not limited to supervised moderate-intensity interventions, and this may explain why significant improvement in HDLs were not a result of either of the meta-analyses.

To explain the variance that existed between the studies in this meta-analysis, meta-regression analyses and subgroup analyses were completed. Meta-regression analyses of total walking dose and the number of weeks did not result in significant variance among the studies for either of the lipids and lipoproteins. However, although walking did not result in significantly improved HDLs, the number of days per week explained some of the between-study variance among the HDL studies. The improvement in HDLs was similar for the majority of the studies, which were studies that reported walking activity of five days per week. The significant variance appeared to primarily exist between the study that reported activity of two days per week (Hopewell, 1989), and study that reported activity of seven days per week (Woolf-May et al., 1999). The Hopewell (1989) study was fully supervised and demonstrated greater improvement in the walking groups than the control group. Conversely, the Woolf-May (1999) study was fully self-reported and demonstrated greater improvement in the control groups than the walking groups. The variance in HDL results for days per week appears to be explained by the difference in overall design of the Hopewell (1989) and Woolf-May (1999), as opposed to the entire sample of studies.

Meta-regression analyses of BMI and year of study explained between-study variance in the lipids and lipoproteins. BMI moderated the results of all the lipids and lipoproteins, and year

of study moderated the results of total cholesterol, triglycerides, and LDLs. In the meta-regression analyses for BMI, the mean difference between the control and experiment groups increased as mean BMI increased. The obese subjects showed a greater improvement in lipids and lipoproteins than the overweight subjects as a result of the walking interventions. One explanation for this finding is that dyslipidemia tends to be higher in obese adults than adults who are overweight (Saydah et al., 2014). The baseline lipid and lipoprotein values were more abnormal for the obese subjects in this meta-analysis than the overweight subjects. Therefore, it appears that the more abnormal the baseline values were of the subjects, the greater the effect of the walking interventions. Although the meta-regression analyses did not result in a statistically significant between-study variance in baseline values for each lipid and lipoprotein, a positive relationship existed between the RMDs and the baseline values. For year of study, the significant between-study variance appeared to exist due to the average BMI of the studies. The year of study ranged from 1987 to 2016, but there were no major differences in the design of the studies that would impact lipid and lipoprotein outcomes. However, it was apparent that most of the studies that had obese subjects (mean BMI $\geq$30 kg/m$^2$) were the studies that were published between 2001 and 2016. Globally, obesity has nearly tripled since 1975 (World Health Organization, 2018), and it is possible that the reason why fewer of the earlier studies (1987-1999) in this meta-analysis had obese subjects is because the obese population (globally) was not as prevalent as it has been in recent years.

For the subgroup analyses, intensity, menopause stage, and type of walking activity (self-reported, supervised, or both) did not have moderating effects on the lipids and lipoproteins. Similar results were also observed in the Kelley et al. (2004) meta-analysis. The majority of the studies in this meta-analysis reported moderate-intensity walking rates, which is recommended

for overall health benefits [American College of Sports Medicine (ACSM, 2014)]. In this meta-analysis, very few studies reported low-intensity walking rates and due to the limited number, these studies could not be included in the subgroup analyses. This resulted in comparing the effects of moderate-intensity walking to the effects of vigorous-intensity walking, which potentially explains why there was no significant difference in the walking intensities. Surprisingly, comparison of the menopause stages did not result in significantly different effects on the outcome variables. Estrogen plays a role in regulating energy metabolism (Bhardwaj et al., 2019) and due to the significant decline of estrogen in post-menopausal women, it would appear plausible that the improvement in lipids would affect the post-menopausal women differently than the pre-menopausal women. However, because exercise upregulates lipid metabolism (Butcher et al., 2008), this may explain why no significant difference between the menopause stage groups existed. Comparison of self-reported, supervised, and a combination of both types of walking activity did not result in a significant difference between the groups. It would appear that studies that had supervised walking activity would have a significantly different effect on the outcome variables than the other groups. However, use of self-reported activity is often a limitation due to social desirability bias (van de Mortel, 2008), which may explain why the results of self-reported activity were similar to the supervised activity and the combined activity.

Subgroup analysis of the continent of the studies explained between-study variance in RMD for LDLs. The continent where the studies were completed resulted in a significant difference between the North American and European studies. The European studies had greater improvement in LDLs than the North American studies. The European walking groups significantly improved in LDLs more than their paired control groups as a result of the walking interventions.

However, for the North American studies, there was no difference in the LDL RMD of the walking groups and their paired control groups. Also, although not statistically significant, there was a trend of greater improvement in the other lipids and lipoproteins in the European studies when compared to the North American studies. One possible explanation for the European studies demonstrating significantly greater improvement in LDLs and greater improvement in the other lipids and lipoproteins than the North American studies, is the European subjects may have been more compliant with their prescribed activity than the subjects in the North American studies. In European countries, 61.47% of adults have reported engaging in the recommended amount of moderate-to-vigorous physical activity (Marques, Sarmento, Martins, & Saboga Nunes, 2015), whereas 32.6% of U.S. adults meet the recommended guidelines for aerobic physical activity (Carlson, Fulton, Schoenborn, & Loustalot, 2010).

Overall, this meta-analysis offers implications for use of walking in overweight and obese women. Significant improvement in total cholesterol and LDLs were observed for a population of women who did not exhibit weight-loss (Median $\triangle$ in BMI= -0.95 $kg/m^2$) as a result of walking at moderate or vigorous intensity about 171 minutes per week (Mean= 171.5 minutes) for 19 weeks (Mean= 19.31 weeks). While improved diet and weight-loss are very important and ultimately essential for improving overall health, this meta-analysis supports promotion of walking, potentially as an exclusive non-pharmacologic therapy, for improving total cholesterol and LDLs in overweight and obese women. However, these findings appear to be implications for overweight and obese women who do not present enhanced risk of developing atherosclerotic cardiovascular disease (ASCVD). Although the median value for LDLs in this sample was abnormal, the value is not indicative of enhanced risk for developing ASCVD ($\geq$160 mg/dL; Arnett

et al, 2019). For adults who do not have LDLs of ≥160 mg/dL, clinicians are advised to recommend lifestyle habits that will improve the condition (e.g. engaging in at least 150 minutes per week of accumulated moderate-intensity or 75 minutes per week of vigorous-intensity aerobic physical activity) as opposed to treating the abnormality with pharmacologic therapy (Arnett et al, 2019). The reduction in LDLs demonstrated in this meta-analysis, support clinical guidelines for preventing ASCVD. The guidelines do not specify recommended LDL reductions for non-pharmacologic therapy, but it is clear that the goal is to normalize LDLs in order to prevent ASCVD. The median baseline value for total cholesterol in this study was relatively normal. However, the improvement in total cholesterol supports clinical guidance for advising regular physical activity to prevent ASCVD in adults who do not exhibit enhanced risk from lipids (Arnett et al., 2019). Therefore, because exclusive walking has demonstrated a reduction in LDLs and total cholesterol in overweight and obese women, it can potentially serve as an exclusive non-pharmacologic therapy for preventing ASCVD in overweight and obese women who have lipid profiles that do not exhibit enhanced risk.

This meta-analysis also demonstrates that BMI plays a significant role in lipid and lipoprotein outcomes; and for obese adults, it is clear that weight-loss yields optimal effects (Haines et al., 2007; Hanson & Jones, 2015; Schulz et al., 2015). However, as demonstrated in this meta-analysis, when significant weight-loss is not obtained, walking at moderate or vigorous intensity an average of 171 minutes per week for 19 weeks aids in normalizing total cholesterol and LDLs.

## Limitations

This systematic review and meta-analysis has some limitations. Due to the inherent nature of the study, it is possible that some qualifying studies may not have been identified for article inclusion. However, both Reviewers completed a thorough search of the scientific literature, per the Cochrane Review protocol (Higgins & Green, 2011).

Another limitation is that one study dominated the overall effects of the main findings. The Guessogo (2016) study mainly contributed to the total cholesterol and LDL meta-analyses having larger and significant effects (significant and greater RMDs between the walking and control groups). The Guessogo (2016) study distinctly observed an obese population (mean BMI= 34.23 $kg/m^2$) who walked a total of 200 minutes per week [20 minute warm-up (low to moderate walking intensity) + 30 accumulated-session minutes (moderate to vigorous walking intensity with 30 minutes of accumulated interval rest) x 4 days per week] for 24 weeks. Per ACSM (2014), 200 to 300 minutes of moderate intensity exercise per week is recommended for overweight and obese populations. Also, all the walking activity was supervised. Therefore, possibly the reason why this study (Guessogo, 2016) dominated the overall RMDs for total cholesterol and LDLs, is because the study had fully supervised sessions that met the exercise recommendations for improving overall health when overweight or obese. In the total cholesterol and LDL meta-analyses, two other studies (Nieman et al., 2002; Ready, 1995) had a similar design of the Guessogo (2016) study, but they did not dominate the results of the overall RMD for the lipid and lipoprotein. If the Nieman et al. (2002) and Ready et al. (1995) studies were individually removed, changes to the RMD would be minor and would remain statistically significant. This may be due to the Nieman et al. (2002) study having a shorter term (12 weeks), or the Ready et

al. (1995) study having both self-reported and supervised walking activity. In addition, the participants in the Nieman et al. (2002) and the Ready et al. (1995) studies were less obese (mean BMI $\leq$32 kg/m$^2$). If more of the sample of studies in the meta-analyses would have observed relatively moderate-obese subjects for at least 24 weeks, with 200 or more minutes of weekly supervised activity, the Guessogo (2016) study would not have possibly dominated the results.

Risk of bias, publication bias, a limited number of studies in some of the subgroup analyses and reporting of intervention compliance were also limitations. Three studies were determined to have high-risk of bias for selective reporting (Musto et al., 2010; Verity & Ismail, 1989; & Woolf-May et al., 1999). However, if these studies were individually removed, changes in the overall effect for total cholesterol and LDLs are minimal and the effect remains statistically significant. Publication bias, which is published research that is unrepresentative of the total population of studies (Borenstein et al., 2009), appeared to be present for total cholesterol. The Duvall and Tweedie's trim and fill adjustment showed publication bias for the Verity & Ismail (1989) study, but removal of this study from the total cholesterol meta-analysis would result in minimal change to the RMD with no statistical effect on the conclusions. A limited number of studies existed for the sub-group analyses. There were few studies that had low-intensity interventions, and few studies that were completed in Asia. These studies could not be included in all of the intensity subgroup analyses, and continent subgroup analyses for triglycerides, HDLs, and LDLs. Also, due to there being only two studies that were completed in Africa, these studies were not included in the continent subgroup analyses for either of the lipids and lipoproteins. Unfortunately, less than 20% of the studies reported intervention compliance or values for the number of minutes that were actually completed by the subjects. The prescribed walking (e.g., 30

minutes/day, 5 days/week) was relied upon for most of the studies in order to determine the intervention dose. However, subgroup analyses of self-reported and supervised activity were completed in an attempt to determine if there was a difference in both groups that may infer how the level of compliance impacted the outcomes. Future studies should ensure that compliance of their subjects is reported.

## Conclusions

Walking aids in normalizing total cholesterol and LDLs in overweight and obese women. Exclusive of diet and weight-loss, walking improves total cholesterol and LDLs under moderate and vigorous intensities. The findings from this meta-analysis support promotion of walking as a non-pharmacologic therapy for vascular health.

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*Denotes studies in the meta-analysis

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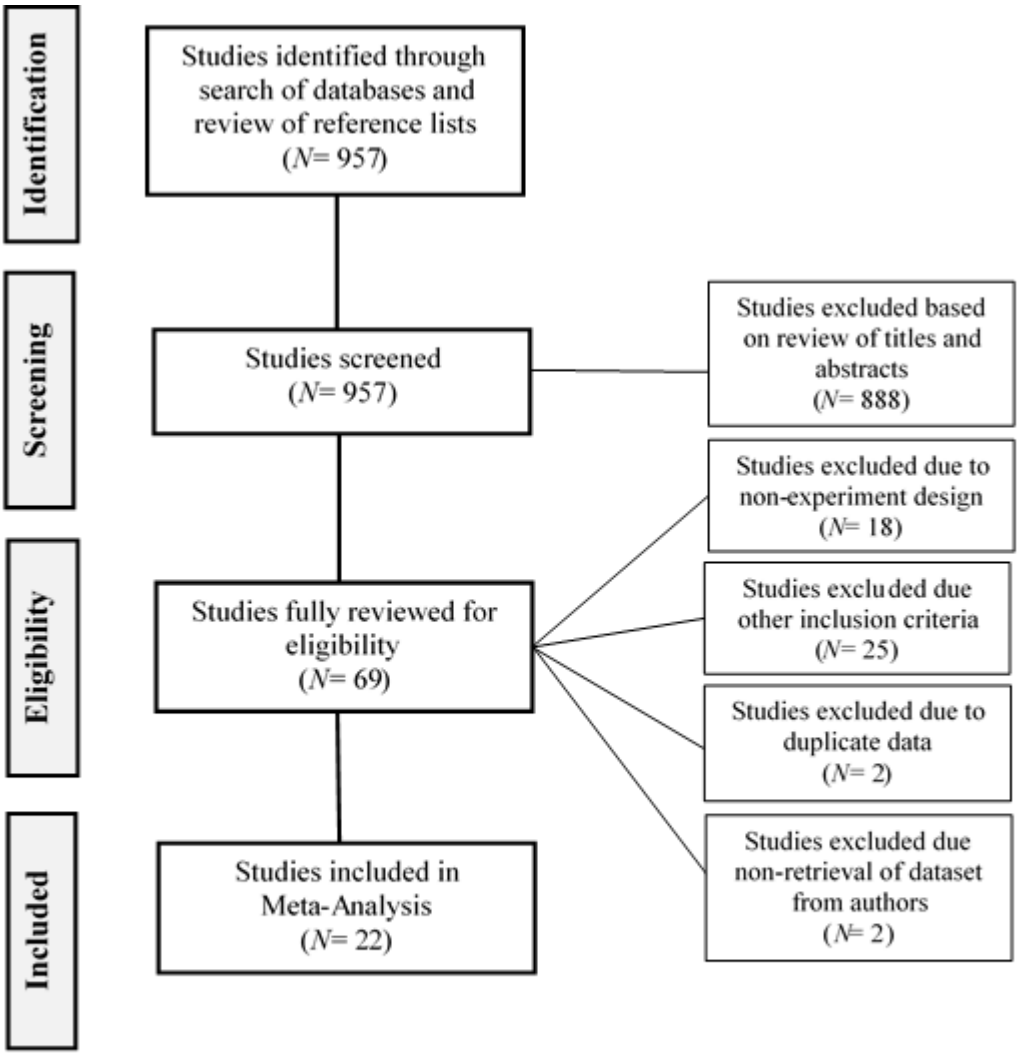
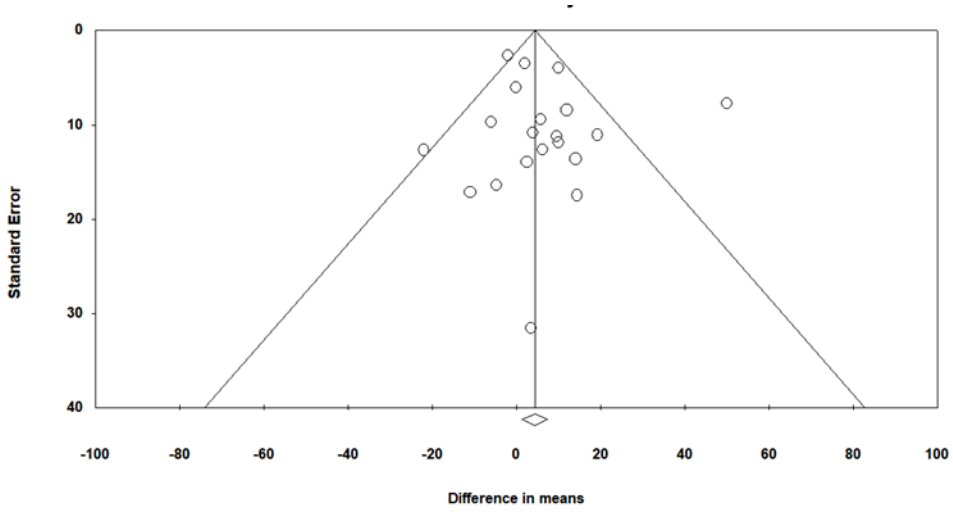
# APPENDICES

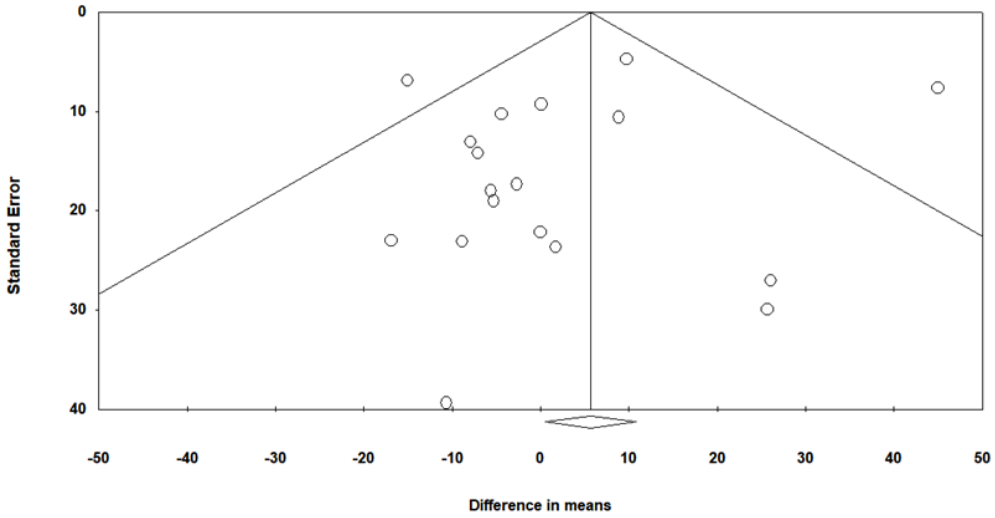
**Appendix A.** PRISMA flowchart of review and selection of studies.



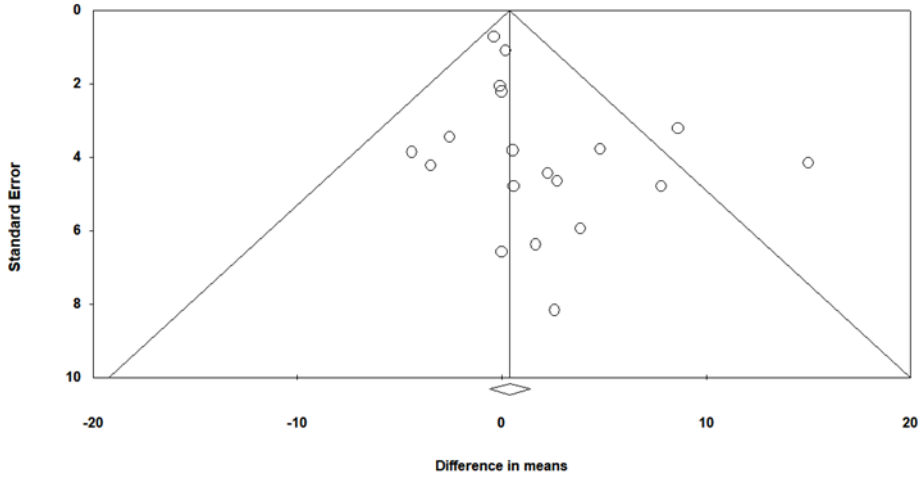
**Appendix B.** Total cholesterol: Funnel plot of standard error by difference in means.




**Appendix C.** Triglycerides: Funnel plot of standard error by difference in means.



**Appendix D.** High-density lipoproteins: Funnel plot of standard error by difference in means.




**Appendix E.** Low-density lipoproteins: Funnel plot of standard error by difference in means.