THE ROLE OF PHYSICAL ACTIVITY ON CARDIOVASCULAR DISEASE RISK FACTORS IN POSTMENOPAUSAL WOMEN

by

Kelley Kathryn Pettee

BS, Athletic Training/Exercise Science, Ithaca College, 1996
MS, Clinical Exercise Physiology, Northeastern University, 1999

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This dissertation was presented

by

Kelley Kathryn Pettee

It was defended on

July 10, 2006

and approved by

Dissertation Advisor:
Andrea M. Kriska, PhD
Associate Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Bret H. Goodpaster, PhD
Assistant Professor, Department of Medicine
School of Medicine, University of Pittsburgh

B. Delia Johnson, PhD
Research Associate, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Lewis H. Kuller, MD
Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Trevor J. Orchard, MBBCh, MMEdSci
Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh
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Cardiovascular disease (CVD) is the leading cause of death among women in the US. CVD is still thought to be a “man’s disease” and remains underappreciated by the public and under treated by health-care providers. Yet, unlike men, a large proportion of deaths attributable to CVD occur in asymptomatic women, making early detection and diagnosis difficult. Therefore, both the development of primary CVD prevention strategies to decrease the risk of CVD and screening tools that will aid in the early detection of women who are at increased risk for CVD has major public health implications.

Hormone therapy (HT) has been shown to beneficially affect adverse changes to CVD risk factors that occur during menopause; however, HT is no longer indicated for general CVD prevention. Increased physical activity (PA) levels, either separately or as part of a lifestyle intervention, may decrease CVD risk in women; however, previous reports have not adequately accounted for concurrent changes in HT status.

Strategies for primary CVD prevention and early detection in postmenopausal women were examined using 508 women from the Woman on the Move through Activity and Nutrition (WOMAN) study. At baseline, PA was found to be related to more favorable lipid and lipoprotein subclass levels; however, some of these associations were influenced by current HT use. Results at 18 months suggested that a lifestyle intervention was effective for general CVD risk factor reduction regardless of HT continuation or discontinuation. Additionally, lifestyle
appeared to attenuate increases in lipid levels that resulted from discontinuing HT. Finally, a simple walking endurance test may provide supplemental information when ascertaining CVD risk in women.

In the post-WHI era, concern and confusion about the risks associated with HT has left women and health-care providers searching for alternative means to decrease risk of CVD. Findings from the current report suggest that a non-pharmacological approach for CVD risk factor reduction is both safe and effective for primary CVD prevention in postmenopausal women. In light of the current controversies surrounding the use of HT, the promotion of healthy lifestyle behaviors for CVD risk factor reduction has important public health implications.
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PREFACE

“God grant me the serenity to accept the things I cannot change; courage to change the things I can; and wisdom to know the difference.” –Reinhold Niebuhr.

This degree is the accomplishment of many important people in my life. I would like to thank my advisor, Dr. Andrea Kriska, for teaching me and providing me with opportunities that few students are lucky enough to get and Dr. Lewis Kuller for the opportunity to work as a graduate student researcher on the WOMAN Study. My committee members, Drs. Bret Goodpaster, Delia Johnson, and Trevor Orchard, have my sincere appreciation for their time, input, and dedication to this project. I am also very gracious for the support of the WOMAN study staff and other key staff members in the department. Finally, I would like to thank my many mentors, particularly Dr. Marilyn Cairns, who was instrumental to the achievement of this degree.

I would like to thank my family and close friends for all of their love and support. Mom and Dad, my successes in life are yours as well, I would not be where I am today without you. Thank you Mike, Sara, Amy and Julie for your humor and encouraging words that helped me keep going. Thank you Nana and Gramps (Pettee) and Gramma and Grampa (Gault) for pulling strings for me in heaven. Darcy, I am so very grateful to have you as my best friend, thanks for putting up with me! Thank you Kristi, I couldn’t have shared an office with anyone else. Mark, thank you for the good times and support through the difficult times. Thank you Jen, Molly, Rachel, Beth, and others for your encouragement and support over the past 4 years.
1 INTRODUCTION

1.1 MENOPAUSE AND CARDIOVASCULAR DISEASE RISK

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among women in westernized countries. In the United States (U.S.) alone, more than half a million women die each year as a result of CVD and CVD mortality rates continue to rise\(^4\). In addition, a large proportion of deaths attributable to CVD occur in women with no previous symptoms, making early detection and diagnosis difficult\(^1,2\).

The escalating rates of CVD observed in older, postmenopausal women may be related to the substantial adverse cardiovascular changes that occur as a woman transitions from pre- to post-menopausal status. In many women, CVD risk factors, including dyslipidemia, hypertension, abdominal adiposity, and insulin resistance develop during the menopausal transition\(^5,6\). The alterations in lipid metabolism caused by estrogen deficiency are thought to be a substantial component of CVD development in postmenopausal women. In addition to the adverse changes in CVD risk factors, detrimental lifestyle changes, such as an increase in sedentary behaviors, that are common as one ages have been suggested to play a critical role in CVD development\(^3,7-10\).
1.2 HORMONE THERAPY AND CARDIOVASCULAR DISEASE

Results of past observational epidemiological studies suggested that postmenopausal women taking hormone therapy had a 40-50% reduction of CVD when compared to non-hormone therapy users. However, recent evidence from randomized clinical trials has failed to validate the proposed cardio-protective benefits of hormone therapy. The Heart and Estrogen/progestin Replacement Study (HERS), found that among postmenopausal women with documented CVD, there was an increased risk of future CVD events within the first year of study randomization among hormone therapy users. Similar findings were observed in the Women’s Health Initiative (WHI). The WHI consisted of three separate study arms: 1) low-fat dietary pattern, calcium and vitamin D supplementation, 2) combined estrogen and progestin, and 3) estrogen only. In 2002, the combined estrogen and progestin arm was terminated early due to growing evidence that women without previous CVD who were randomized to receive the combined hormone therapy had an increased risk of CVD, stroke, pulmonary embolism, and breast cancer. In 2004, the estrogen alone arm was discontinued as well because results suggested that estrogen therapy increased the risk of stroke and did not appear to reduce the risk of CVD. Findings from these studies have culminated in changed recommendations for prescription and distribution of hormone therapy in postmenopausal women. Current guidelines recommend against the routine use of combined estrogen and progestin or unopposed estrogen for the prevention of cardiovascular disease in postmenopausal women.

Beyond CVD incidence, hormone therapy has also been shown to impact a number of CVD risk factors. In general, hormone therapy has been suggested to alter the lipid profile in postmenopausal women. When compared to non-hormone therapy users, women taking hormone therapy consistently had decreased LDL and increased HDL and triglyceride levels as
measured by traditional measures\textsuperscript{3, 7, 9, 18, 19}. All can be considered beneficial changes with the exception of elevated triglycerides. Additionally, results from the combined estrogen and progestin arm of the WHI study suggested that women randomized to hormone therapy had greater reductions in both insulin and glucose levels. However, systolic blood pressure among the group receiving combination therapy was 1 mmHg higher at the first year follow-up visit and remained 1 to 2 mmHg higher at subsequent follow-up visits. Diastolic blood pressure did not differ between groups\textsuperscript{20}. This recent evidence from randomized clinical trials has failed to validate the cardio-protective benefit of hormone therapy. Therefore, other strategies need to be pursued in order to decrease CVD risk in women.

1.3 PHYSICAL ACTIVITY LEVELS IN POSTMENOPAUSAL WOMEN

One possible strategy for CVD prevention among older women may be to increase physical activity levels. Participation in regular amounts of physical activity has been demonstrated to play a vital role in the health and well-being of individuals of all ages\textsuperscript{21}. Regular physical activity levels may help prevent or control many chronic diseases such as cardiovascular disease\textsuperscript{22-24}, diabetes\textsuperscript{25-28}, cancer\textsuperscript{29, 30}, depression\textsuperscript{31, 32}, and functional decline\textsuperscript{33, 34}.

Despite the well established benefits, only 38.6\% of adults reported being physically inactive during their leisure time, defined as never engaging in any light, moderate, or vigorous leisure time physical activity. Additionally, over 68\% of Americans did not meet the current minimum physical activity guidelines\textsuperscript{35}, defined as 30 minutes of moderate intensity activity, such as that of a brisk walk, on most if not all days of the week\textsuperscript{21}.
Specific subgroups of the population, such as women, minorities, and the elderly are less likely to participate in regular amounts of physical activity\textsuperscript{35}. Older, postmenopausal women are among the least active subgroups in America\textsuperscript{35}. Higher rates of physical inactivity are particularly alarming due to the demonstrated beneficial link between physical activity and a number of conditions that affect older women.

Previous reports suggest that individuals with regular physical activity levels have a reduced risk of developing CVD\textsuperscript{21-24, 36}. Inactive individuals are considered twice as likely to develop CVD as their active counterparts\textsuperscript{36}. The inverse association between physical activity and CVD development may be due in part to the beneficial role of physical activity on the underlying etiology of cardiovascular risk factors\textsuperscript{6, 37}. As a result, physical inactivity has been identified as a major modifiable risk factor for CVD development due in part to numerous associated physiological benefits\textsuperscript{38}.

In general, physical activity has been shown to improve myocardial contraction, decrease resting heart rate, and increase stroke volume\textsuperscript{39, 40}. Additionally, there is improvement in endothelial function and flow-mediated dilation, increase in coronary artery formation and a decrease in clotting as a result of physical activity\textsuperscript{40-42}. Most of the past studies suggesting an inverse relationship between physical activity and CVD risk, many earlier studies were performed in men. The assumed benefit of physical activity on CVD development in women was extrapolated from such data\textsuperscript{43}. Only recent investigations on the relationship between physical activity and CVD development have specifically targeted older women. Current evidence suggests that there is, in fact, a beneficial relationship between physical activity and CVD development among older, postmenopausal women\textsuperscript{44-50}. 

4
The inverse relationship between physical activity and CVD may be explained by the reduction of cardiovascular risk factors (ie. hypertension, diabetes) in women who are physically active. However, the relationship between physical activity and lipids in postmenopausal women has been inconclusive. Some studies have demonstrated a beneficial relationship between physical activity and lipids, while others suggest no association. To complicate matters, the association with physical activity may differ depending upon the specific lipoprotein in question. For example, some studies may suggest a positive association between physical activity and HDL levels; however, in the same investigation find no relationship between physical activity and other lipids.

The inconsistent findings on the relationship between physical activity and lipids in postmenopausal women may be due to a number of factors. For one, there were differences in the assessment of physical activity. For example, some studies on physical activity and lipids assessed fitness levels using maximum VO$_2$ testing, rather than physical activity levels. Secondly, the study population differed in their hormone therapy use. Some studies included women taking hormone therapy, while others specifically excluded hormone therapy users. In addition, when controlling for hormone therapy during statistical analyses, some studies adjusted for current use of hormones, while others adjusted for past hormone therapy use.

The relationship between physical activity and lipids in postmenopausal women may be better clarified using specific lipoprotein subclasses and not traditional cholesterol measures. Specific lipoprotein subclasses, such as LDL size, total and small LDL particle number may relate better to cardiovascular disease development than traditional measures. Nuclear magnetic spectroscopy (NMR) is a relatively new technique that directly measures lipoprotein
subclasses. Little is known about the relationship between physical activity levels and lipoprotein subclasses and this relationship has yet to be explored in postmenopausal women on and off HT.

Despite the inconclusive relationship between physical activity and lipid levels, physical activity has been suggested to be beneficially related to other CVD risk factors. Regular activity improves the sensitivity of liver, skeletal muscle, and adipose tissue to insulin\textsuperscript{37-39}. Furthermore, physical activity decreases both overall body weight and visceral fat accumulation\textsuperscript{21, 60-63}. It is also well established that physical activity decreases blood pressure\textsuperscript{21, 60, 64} and favorably alters markers of the inflammatory process\textsuperscript{65-69}.

In addition to examining the independent associations between physical activity and CVD risk factors, more recent randomized clinical trials have explored the combined effect of physical activity, diet, and weight loss (lifestyle based approach) on CVD risk factor reduction and/or chronic disease prevention. Results from randomized clinical trials have demonstrated success in populations at risk for diabetes\textsuperscript{25-28} and heart disease\textsuperscript{70}; however, few studies incorporating lifestyle changes have targeted women at or after menopause. The Women’s Healthy Lifestyle Project (WHLP), a randomized clinical trial, examined the effects of a lifestyle intervention on CVD risk factor change from pre- to post-menopause\textsuperscript{71, 72}. Results from WHLP demonstrated that a lifestyle based approach was successful at preventing weight gain\textsuperscript{73} and rise in LDL-C levels\textsuperscript{74} among women in peri- to post-menopause. However, these previous reports did not account for concurrent changes in HT status, an issue which has become particularly relevant in the post-WHI era.
The identification of women who are at an increased risk of incident CVD is as important 
to primary CVD prevention efforts. As stated above, a large proportion of CVD related deaths 
occur in women with no previous symptoms\textsuperscript{1,2}. The identification of asymptomatic women who 
are at increased risk for CVD also has important public health implications. Past 
epidemiological studies have suggested that exercise capacity and/or cardiovascular fitness is an 
independent predictor of cardiovascular events and death among asymptomatic women\textsuperscript{2,75}. 
However, the gold standard technique used to evaluate cardiovascular fitness levels [maximal 
oxygen uptake (VO\textsubscript{2} max)] may not be financially practical in large epidemiological studies due 
to time constraints, staff burden, high equipment costs, and safety concerns\textsuperscript{76}. Tests of walking 
endurance, such as the long distance corridor walk (LDCW) have been substituted for this gold 
standard measure in older populations with promising results. However, few data are available 
regarding the applicability of this test in middle-aged, postmenopausal women.

1.4 STUDY GOAL

The identification of safe and effective primary CVD prevention strategies and screening tools 
that will aid in the early detection of asymptomatic women who are at increased risk for incident 
CVD has major public health implications. Therefore, the specific aims of the current 
investigation are to: 1). examine the cross-sectional relationship between physical activity, lipids, 
and lipoprotein subclass levels by current HT use, 2). determine the effect of lifestyle 
intervention on adverse CVD risk factor changes that may result from HT discontinuation, and 
3). investigate the utility of a walking performance protocol among a cohort of overweight, 
middle-aged postmenopausal women. To accomplish these goals, we utilized a cohort of 508
postmenopausal women, aged 52 to 62, enrolled in the Women On the Move through Activity and Nutrition (WOMAN) Study. The WOMAN study is a randomized clinical trial of primary cardiovascular disease prevention in Pittsburgh, Pennsylvania (PA). Eligibility criteria for enrollment into the study included waist circumference $\geq 80$ centimeters (cm), body mass index between 25-39.9 kilograms per meters squared ($\text{kg/m}^2$), not currently taking lipid lowering drugs, having a low density lipoprotein (LDL-c) level between 100-160 milligrams per deciliter (mg/dL), no physical limitation that would preclude walking, no known diabetes, and no diagnosed psychotic disorder and depression.

The recruitment of eligible WOMAN study participants was directly impacted by publication of the results from the combined estrogen progestin arm of the WHI and resulted in a natural experiment. Initial entry criteria for the WOMAN study required potential participants to be current HT users with at least two years of prior use. Approximately midway through the recruitment process, results were publicized from the estrogen/progestin (E+P) arm of the WHI trial indicating adverse effects among HT users$^{13}$. In response to the WHI findings, the eligibility criteria in the WOMAN study were modified to include women with a recent history of HT use as it was deemed unethical to require potential participants to use HT. As a result, 204 (40.2%) of the WOMAN study participants were not current HT users at baseline. The changes in these eligibility criteria have provided the unique and timely opportunity to investigate the separate and combined role of physical activity as part of a lifestyle intervention for CVD risk factor reduction by current HT use and during HT discontinuation.

Using the WOMAN study cohort, we have the opportunity to clarify the cross-sectional associations between leisure physical activity and lipids using specific lipoprotein subclass measures and investigate how these relationships may be influenced by current HT use. In
addition to examining the independent contribution of physical activity for primary CVD prevention, we will also be able to investigate the effectiveness of a lifestyle intervention that includes physical activity in attenuating adverse changes to CVD risk factors that may develop as a result of discontinuing HT. Finally, tests of walking endurance have been used with promising results for estimating fitness levels, functional ability, and general health status in older adults. However, little is known regarding the applicability of these tests in younger populations. Data from the WOMAN study will allow us the opportunity to investigate the usefulness of the long distance corridor walk (LDCW) in middle-aged, postmenopausal women.

Specifically, the study meets the following objectives:

**Paper 1:** Examine the cross-sectional relationship between physical activity levels and lipoprotein subclasses by hormone therapy status at baseline.

a. It is hypothesized that leisure physical activity will be beneficially related to some of the lipoprotein sub-classes in postmenopausal women; however, there will be a few lipoprotein subclasses in which physical activity is only significantly related in women not taking hormone therapy.

**Paper 2:** To determine if a lifestyle intervention promoting weight and waist circumference reduction through beneficial physical activity and dietary practices can attenuate unfavorable CVD risk factor changes that are likely to occur as postmenopausal women discontinue hormone therapy (HT) use.

a. It is hypothesized that discontinuation of hormone therapy has negative consequences on many CVD risk factors.

b. A lifestyle intervention will attenuate these negative consequences of discontinuing hormone therapy with regards to many CVD risk factors.
Paper 3: To determine the utility of the LDCW as a measure of health status in middle-aged, postmenopausal women.

a. Walking performance, more specifically walk time, will be significantly related to demographic factors, anthropometric measures, subjective and objective measures of physical activity, and CVD risk factors in postmenopausal women.
2 REVIEW OF LITERATURE

In this literature review, the results of studies that have examined the relationship between physical activity (separately and as part of a lifestyle intervention), cardiovascular disease risk factors, and hormone therapy in postmenopausal women are presented. In addition, the results of investigations that have utilized tests of walking endurance to determine associations with mortality and incident CVD are briefly outlined. The strengths and weaknesses of the existing literature that lead to the development of the current project will also be discussed.

2.1 MENOPAUSE AND CARDIOVASCULAR DISEASE RISK

Currently, cardiovascular disease (CVD) is the leading cause of morbidity and mortality among older women and mortality rates continue to rise. Coronary heart disease (CHD) accounts for the majority of CVD deaths in women and disproportionately affects racial and ethnic minorities. In the past, the number of CVD related deaths was strikingly higher in men when compared to women. Since 1984, the gap between male and females deaths attributed to CVD has narrowed dramatically. The reasons for this gender discrepancy are not well understood; however, studies have suggested that the clinical presentation of CVD in women differs from that of men. A large proportion of deaths attributable to CVD occur in women with no previous symptoms, making...
early detection in women particularly challenging. Risk factors suggested to be specific to
development of CVD in women include dyslipidemia, inflammation, and insulin resistance\textsuperscript{77}.

Menopause is defined as the permanent cessation of menses. The menopausal transition
defines the period of time in a woman’s life between her pre- and post-menopausal years.
During this time, levels of endogenous sex hormones such as estrogen decrease. The lack of
estrogen is thought to be related to unfavorable changes in cardiovascular risk factors. In many
women, CVD risk factors, including dyslipidemia, hypertension, abdominal adiposity, and
insulin resistance begin to develop during the menopausal transition\textsuperscript{5, 6}. These changes have
been suggested to explain the increase in development of CVD in older, postmenopausal women.

One consequence of estrogen loss at menopause is an increase in centralized, or intra-
abdominal fat\textsuperscript{78}. Higher intra-abdominal fat has been identified as an important CVD risk factor,
independent of overall obesity\textsuperscript{79}, due in part to its role in the development of dyslipidemia,
inflammation, and insulin resistance\textsuperscript{6}. Furthermore, centralized adiposity is associated with a
greater risk for type 2 diabetes, higher triglyceride levels, and greater number of atherogenic,
small, dense LDL particles\textsuperscript{80}.

Alterations in lipid metabolism caused by the excess in intra-abdominal fat are thought to
contribute to the increase in CVD development in postmenopausal women. The proposed
mechanism by which centralized fat stores increase risk of dyslipidemia is outlined briefly. It
has been suggested that excess intra-abdominal fat is associated with an increase in insulin
resistance, free fatty acid (FFA) levels, and decreased adiponectin (an adipocyte-derived
peptide). These factors contribute to the increased secretion of apolipoprotein B (apo B)
containing particles, which subsequently lead to high triglyceride levels, as well as an increase in
hepatic lipase activity (liver enzyme). The increase in hepatic lipase activity results in a
preponderance of small, dense LDL particles, which are thought to be atherogenic, and a reduction in larger, anti-atherogenic HDL particles.  

The increase in intra-abdominal fat is also associated with increased levels of inflammatory markers, including C-reactive protein (CRP). Increased CRP levels have been shown to be a strong predictor of future cardiovascular events. Centralized adiposity is also directly related to insulin resistance and compensatory hyperinsulinemia, independent of total body fat.

The adverse changes to cardiovascular risk factors among postmenopausal women, such as the development of dyslipidemia, are demonstrated in results published from the Healthy Women Study (HWS). HWS was designed to investigate the changes in biological characteristics of a woman as she transitions through menopause. At study entry, all participants were between the ages of 42 and 50 years and pre-menopausal. Following the baseline assessment, women were asked to report their menstrual status on a monthly basis. A woman was considered postmenopausal when she stopped menstruating and/or had taken hormone therapy for 12 consecutive months. Study participants were re-evaluated at that time and 2, 5, and 8 years after menopause. Changes in cardiovascular risk factors were then compared during the perimenopause (defined as premenopause to 1 year after cessation of menses) and early postmenopause (defined as 1 to 5 years after the menopause). Results suggested that perimenopause was associated with increases in LDL cholesterol, triglycerides, and body mass index, while postmenopause was associated with increases in systolic blood pressure, pulse pressure, and fasting glucose.
As mentioned previously, the lack of estrogen that accompanies menopause is related to a number of CVD risk factors, including dyslipidemia, inflammation, and insulin resistance. As a result, the use of exogenous hormone therapy was thought to be a cardio-protective strategy in postmenopausal women. Earlier observational studies supported the beneficial relationship between hormone therapy use and prevention of CVD\textsuperscript{84-89}. A meta-analysis of epidemiological studies suggested that overall hormone therapy users had a 40-50\% reduction of CVD risk when compared to non-hormone therapy users \textsuperscript{11}. However, recent evidence from randomized clinical trials has failed to validate the proposed cardio-protective benefits of hormone therapy.

The evidence for the relationship between hormone therapy and cardiovascular disease in postmenopausal women is presented in table 2.1 by type of study design. Of the five hospital based case/control studies, one demonstrated a positive association \textsuperscript{90}, two a negative association \textsuperscript{91, 92}, and two investigations suggested no association between hormone therapy and cardiovascular disease development \textsuperscript{93, 94}. Population-based case/control studies found more promising results. Of the eleven studies presented, nine found a negative association \textsuperscript{95-103} and only two found no association between hormone therapy and cardiovascular disease development \textsuperscript{104, 105}. 
Table 2-1: Evidence for the relationship between hormone therapy and cardiovascular disease prevention

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Association</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Case-Control (Hospital Based)</strong></td>
<td>0/+/-/0/-</td>
<td>Rosenberg94; Jick90; Jick91; Rosenberg94; Szklo92</td>
</tr>
<tr>
<td><strong>Case-Control (Population Based)</strong></td>
<td>+/-/-/-/-/0/+/-/-/0</td>
<td>Talbott93; Pfeffer96; Ross91; Bain96; Adam99; Beard100; Thompson104; Psaty101; Newton102; O'Keefe103; Sidney105</td>
</tr>
<tr>
<td><strong>Cross-Sectional</strong></td>
<td>+/-/-</td>
<td>Sullivan108; Gruchow107; McFarland108</td>
</tr>
<tr>
<td><strong>Prospective</strong></td>
<td></td>
<td>Hammond109; Lafferty110; Stampfer111; Wilson99; Bush112; Petitti113; Criqui114; Henderson115; Croft116; Hernandez117; Sullivan118; Henderson119; Stampfer120; Wolf121; Sullivan122; Grodstein123; Alexander124; Hechtbert125; Grodstein126</td>
</tr>
<tr>
<td><strong>Randomized Clinical Trial</strong></td>
<td>-0/0/+/++/+</td>
<td>Nachtigall125; Hulley126; Herrington129; Waters130; Clarke131; Rossouw13; Anderson134</td>
</tr>
</tbody>
</table>

+ indicates positive association (hormone therapy users had an increased CVD risk); - indicates negative association (hormone therapy users had a decreased CVD risk); 0 indicates no association.

The limitations of the case-control study design itself may partially explain the inconsistent findings that are presented in table 2.1. Case-control studies have a number of limitations, including the possibility of recall bias. For example, it may be difficult for a woman to accurately recall the correct type, dosage and/or number of years that she had taken hormone therapy. In addition, case-control studies often rely on existing medical records and proper selection and enrollment of an appropriate control group. This is especially true in hospital based case-control studies where the distribution of a particular exposure, in this case hormone therapy, may not reflect the distribution of the hormone therapy in the general population132.

As presented in table 2.1, all three of the cross-sectional studies demonstrated a negative relationship between hormone therapy and CVD. The results from these studies suggest that...
current hormone therapy users had a decreased risk of cardiovascular disease when compared to non-hormone therapy users\textsuperscript{106-108}.

The cross-sectional study design eliminates some of the restrictions of other study designs including case-control and prospective studies. As compared to case-control studies, cross-sectional study participants no longer have to recall hormone use and are typically defined as current hormone therapy users or non-users. Also, cross-sectional studies do not require the use of an appropriate control group. These factors may partially explain the consistent findings from the cross-sectional studies. Similarly, cross-sectional studies are not subject to limitations that are encountered when using prospective study designs. In cross-sectional studies, there are no issues on misclassification of hormone therapy status, which may affect the results of prospective studies.

Although, all three cross-sectional studies presented in table 2.1 suggested a negative association between hormone therapy and CVD, they are subject to a number of limitations. Cross-sectional studies cannot establish a temporal relationship between hormone therapy use and CVD. Also, prevalent, rather than incident, cases of CVD are identified; therefore, a relationship between hormone therapy use and CVD may be associated with survival rather than risk of development of the disease\textsuperscript{132}.

Table 2.1 also presents the prospective studies that examined the relationship between hormone therapy and cardiovascular disease in postmenopausal women. The results of these studies are broken down into prospective studies that included a group of non-hormone therapy users and those that included hormone therapy users only. Of the nineteen prospective studies that included a group of non-hormone therapy users, fifteen demonstrated a negative relationship\textsuperscript{109-114, 119-123} and one a positive relationship\textsuperscript{89} between hormone therapy use and cardiovascular
disease risk. The three remaining prospective studies included a group of postmenopausal women that were non-hormone therapy users. These three studies found mixed results depending upon whether the woman was a new, current, or prior hormone therapy user. All three of these studies, suggested that new users had an increased risk of developing CVD, while prior or current hormone therapy users showed no additional benefit beyond non-hormone therapy users\textsuperscript{84, 124, 125}. Two studies presented in table 2.1 excluded non-hormone therapy users and demonstrated a negative association between hormone therapy and CVD\textsuperscript{126, 127}.

Prospective study designs avoid the issues that affect other study designs. One important benefit of prospective study designs is that a temporal relationship between hormone therapy use and CVD risk can be established when investigating this relationship. However, as mentioned previously, prospective studies in which the exposure is only measured at one time point, may have problems with misclassification of hormone therapy status and may negatively impact the study results\textsuperscript{132}. This may be one possible explanation for those prospective studies that did not suggest a negative association between hormone therapy and CVD.

The evidence from randomized clinical trials is far more conclusive than observational studies. The randomization process done in many clinical trials ensures that the study groups will be comparable in all respects except for hormone therapy status. Therefore, hormone therapy use and risk of CVD can be more clearly studied, without the known and unknown influence of potential confounding factors\textsuperscript{132}. An early randomized clinical trial found a negative association between hormone therapy and CVD risk\textsuperscript{128}. However, after ten years of follow-up, only 4 of the 168 total women randomized developed CVD. The negative association that was suggested by this early study may have been due to the limited sample size as well as
the low number of cardiovascular events that were observed. Therefore, results from this randomized clinical trial may be difficult to interpret.

Evidence from recent randomized clinical trials has failed to validate the results suggested by past observational studies. The Heart and Estrogen/progestin Replacement Study (HERS), a secondary CVD prevention trial, found that among postmenopausal women with documented CVD there was an increased risk of CVD within the first year of study randomization for women randomized to hormone therapy\(^\text{12}\). Two additional secondary prevention studies found no association between hormone therapy and progression of coronary atherosclerosis\(^\text{129, 130}\), while another found an increased risk of CVD among users of a transdermal estrogen patch\(^\text{131}\).

Primary CVD prevention randomized clinical trials were conducted in addition to secondary prevention trials. The Women’s Health Initiative (WHI) was the foremost primary CVD prevention trial conducted in postmenopausal women. The WHI focused on defining strategies that could potentially decrease CVD, breast and colorectal cancer, and fractures risk in postmenopausal women. The WHI enrolled 161,809 postmenopausal women, aged 50 to 79 years, between 1993 and 1998 across 40 clinical centers in the United States. Eligible study participants were randomized into one of three separate study arms: 1) low-fat dietary pattern, calcium and vitamin D supplementation, 2) combined estrogen and progestin hormone therapy, and 3) hormone therapy consisting of estrogen only\(^\text{13}\).

The primary outcome for the estrogen plus progestin arm of the WHI was CHD. CHD was defined as acute myocardial infarct (MI) requiring overnight hospitalization, silent MI determined from serial electrocardiograms, or CHD death. The study population for this arm of the clinical trial included 16,608 women of which 8,506 received conjugated equine estrogens
(0.625 mg/d, plus 2.5 mg/d medroxyprogesterone acetate) and the remaining 8,102 were given a placebo. Formal monitoring began in 1997. In 1999 the data safety monitoring board (DSMB) observed small, early adverse effects in cardiovascular outcomes, but none of the disease specific boundaries had been crossed. Approximately three years later (2002), the DSMB observed that the adverse effects in cardiovascular diseases persisted, although these results were still within monitoring boundaries. However, at this point, the boundary for breast cancer incidence had been crossed. Based on these data, the DSMB concluded that the evidence for breast cancer harm, along with the increase in CHD and other cardiovascular disease outcomes, outweighed the benefit of reduced fractures and colorectal cancer. As a result of these findings, the combined estrogen and progestin arm was terminated early after a mean follow-up of 5.2 years (planned duration was 8.5 years)\textsuperscript{13}.

In 2004, the final results from the estrogen plus progestin arm of the WHI were published and provided an updated analysis of coronary endpoints (acute MI, silent MI, CHD death, angina, acute coronary syndromes, and congestive heart failure). Women randomly assigned to receive estrogen plus progestin had a 24\% higher risk of CHD when compared to women in the placebo group. Furthermore, the cumulative hazard rates of CHD showed an elevated risk among women taking estrogen and progestin soon after randomization and rates did not begin to converge between groups until 6 years post randomization. Additional analysis was performed to determine whether certain subgroups of women were at a higher or lower risk for CHD with estrogen and progestin based on baseline levels of lipid, inflammatory and thrombotic biomarkers. Only women randomized to hormone therapy, with higher levels of LDL cholesterol at baseline, had evidence of a pattern of hazard ratios for CHD that were different from patterns found among other women (Manson, 2003).
Similarly, the primary outcome for the estrogen only arm of WHI was CHD development. Again, CHD was defined as acute myocardial infarct (MI) requiring overnight hospitalization, silent MI determined from serial electrocardiograms, or CHD death. The study population for this arm of the clinical trial included 10,739 postmenopausal women with prior hysterectomy. Women were randomly assigned to receive either conjugated equine estrogens \([n=5310 \ (0.625 \text{ mg/d})]\) or placebo \([n=5429]\). As with the combined hormone therapy arm, formal monitoring of disease rate comparisons began in 1997 by the DSMB. In early 2000 and again in 2001, the DSMB recommended that participants in both arms of the study be informed of the early increases in CHD, stroke, and blood clot development that was found in women taking either form of hormone therapy. After the early termination of the estrogen and progestin arm, participants in the estrogen alone arm were notified about the increase in breast cancer that was observed in the E+P arm. In 2004, after additional review, the National Institutes of Health (NIH) decided to stop the intervention phase of the trial on the basis that estrogen increased the risk of stroke and did not appear to affect CHD development\(^{14}\).

Despite the benefits suggested in observational studies, the negative results generated from both the primary and secondary prevention randomized clinical trials are far more conclusive. Only randomized clinical trials can establish the efficacy and safety of hormone therapy use for prevention CVD in postmenopausal women. As a result of the negative findings, current guidelines recommend against routine hormone therapy use for chronic conditions, including CVD. Furthermore, current hormone therapy users are currently advised to taper doses and ultimately discontinue use\(^{15}\).

Hormone therapy has been shown to impact a number of cardiovascular risk factors. In the estrogen and progestin arm of the WHI, women randomly assigned to hormone therapy had
greater reductions in glucose and insulin levels. Also, body weight and waist circumference were lower among women taking hormone therapy; however, waist to hip ratio did not differ between groups. Among women receiving hormones, systolic blood pressure was 1 mmHg higher at the first year follow-up visit and remained 1 to 2 mmHg higher at subsequent follow-up visits. Diastolic blood pressure did not differ between groups²⁰.

Hormone therapy use has also been suggested to improve the overall lipid profile of older, postmenopausal women. Past studies have shown that, estrogen users had lower levels of LDL cholesterol levels and higher HDL cholesterol and triglyceride levels than non-users³, ⁷, ⁹, ¹⁸, ¹⁹. All can be considered beneficial changes with the exception of the rise in triglyceride levels. Triglycerides have been identified as an independent risk factor for CVD among women¹⁸, ¹³³.

Lipoproteins comprise several distinct subclasses that differ in size, density, and composition¹⁸, ¹³³, ¹³⁴. Disease risk is typically based on the indirect measurement of cholesterol that is carried by these lipoproteins. However, the amount of cholesterol that the particles actually contain varies from person to person due to differences in particle core composition and diameter. It has been suggested that CVD risk may be better quantified using specific lipoprotein subclasses measurement as opposed to traditional methods¹³⁴, ¹³⁵. Traditional methods simply quantify the cholesterol carried within the particle as a surrogate marker for the actual lipoprotein concentration¹³⁴. Nuclear Magnetic Resonance (NMR) spectroscopy allows lipoproteins and their subclasses to be rapidly and directly quantified in order to provide a more accurate assessment of risk factors relating to CVD development among postmenopausal women. Past studies have suggested that LDL particle size, total and small LDL particle number is associated with incident CVD among older women⁵⁹.
Although hormone therapy users tend to have lower LDL cholesterol levels than non-users, estrogen has been found to also decrease LDL particle size\textsuperscript{136, 137}. Small LDL particles have been shown to be more atherogenic than larger LDL particles and are negatively correlated with large HDL levels\textsuperscript{133, 138}. Moreover, small LDL particles have a low affinity to LDL receptors and are more susceptible to oxidative metabolism and binding to arterial wall proteoglycans, setting the stage for atherosclerosis\textsuperscript{139}.

### 2.3 PHYSICAL ACTIVITY ASSESSMENT IN EPIDEMIOLOGICAL STUDIES

Physical activity is a complex behavior and selecting the proper assessment tool(s) is challenging, particularly among free-living populations. The lack of a reasonable gold standard measure and inconsistent use of physical activity terminology has contributed to confusion in this field. Measurement is further complicated by the fact that there are several health-related dimensions of physical activity\textsuperscript{140}, which may require the use of different assessment tools. The qualitative difference among the various dimensions of physical activity contributes to the diversity in the mechanisms behind the relationship of physical activity and specific diseases and, therefore, alter how physical activity should be assessed. When examining the relationship between physical activity and a disease or condition, it is important to focus on the dimension(s) of physical activity that is most likely to be associated with the specific outcome of interest.

Energy expenditure is defined as the exchange of energy required to perform biological work. Components of total energy expenditure include basal metabolic rate, which typically encompasses 50-70\% of total energy, the thermic effect of food, which accounts for another 7-10\% and physical activity\textsuperscript{141}. Physical activity is the most variable component of total energy expenditure...
expenditure and includes structured (sports, leisure, and occupational activity) and non-structured activities (housework, childcare, and activities of daily living).

Although similar, the terms physical activity and exercise have different meanings. Physical activity is defined as any bodily movement produced by skeletal muscles that result in increased energy expenditure\textsuperscript{142}. Therefore, things such as housework, gardening, occupational, and leisure activity may all be considered types of physical activity. On the other hand, exercise is defined as planned, structured, and repetitive bodily movements done to improve or maintain one or more components of physical fitness and is usually associated with sport or conditioning activities\textsuperscript{142}. When differentiating between the two, exercise is a type of physical activity, but not all physical activity is considered exercise. The term physical fitness is also confused with physical activity and/or exercise and can been defined as a set of attributes, such as cardiorespiratory fitness or muscle strength, that individuals have or can achieve that relate to the ability to participate in exercise and/or physical activity\textsuperscript{142}.

Physical activity may be comprised of several different domains, including transportation, sports/leisure, school/occupation, and housework/child or elderly care and may span across an entire continuum of intensity levels. In order to accurately assess physical activity levels, it is essential that the entire spectrum of activity be captured (Figure 2.1)\textsuperscript{143}. It also becomes imperative that the assessment tool elicits information on the types of physical activities that encompass the greatest proportion of energy expenditure in the study population of interest. As illustrated in figure 2.1, the lower end of the physical activity intensity spectrum is comprised of general activities of daily living such as bathing, feeding, and grooming. The remainder of the intensity spectrum is comprised of activities that range in intensity from low to moderate and moderate to high levels. The relative contribution of each of these types of activity
to total energy expenditure in a specific population will vary depending upon the population of interest.

Figure 2-1: Physical Activity Spectrum (Adapted from Kriska, 2000) ¹⁴³

2.3.1 Subjective Measures: Physical Activity Questionnaires

Self-report questionnaires are the most frequently used method of assessing physical activity levels among community-based individuals. Questionnaires vary in their complexity, time frame, and type of activity that is assessed. Each of these considerations will be outlined in more detail in the following section.

2.3.1.1 Complexity

Physical activity questionnaires vary in their complexity, from single item questionnaires to more complex quantitative history questionnaires estimating physical activity over a lifetime. More complex questionnaires, such as recall questionnaires, attempt to survey a wide range of
popular activities over a defined time frame. Recall questionnaires detail the frequency, duration, and types of activities performed during a defined recall period (e.g., past day, week, month, or year)\textsuperscript{144}.

### 2.3.1.2 Time Frame

Subjective questionnaires can either ask about usual activity or inquire about activity performed within the past day, week, month, year, or even over a lifetime. Participants may be asked to use diaries and logs to record activities over 1 day, 3 days, or the past week. Questionnaires focusing on a long time frame, such as 1 year, are more likely to reflect usual activity patterns and have been used extensively in epidemiologic studies. Questionnaires with short time frames have two advantages over those with longer time frames: the estimates are less vulnerable to recall bias and more practical to validate with objective tools. However, assessment over a short time period is less likely to reflect “usual” behavior, as activity levels may vary with seasons or as a result of illness or time constraints\textsuperscript{144}. To obtain the best estimate of physical activity levels, some questionnaires include assessment over both a short and long time period.

### 2.3.1.3 Activity Type

As mentioned previously, physical activity may be comprised of several different domains. Early studies in physical activity epidemiology estimated physical activity performed at work\textsuperscript{145, 146}. However, since physical activity levels at work have continued to decline in most industrialized countries\textsuperscript{36}, assessment of leisure-time physical activity is often assumed to be the best representation of physical activity in a population. For this reason, most contemporary physical activity surveys only assess leisure-time activities that require energy expenditure above that of daily living. Some questionnaires include both leisure and occupational activity
components to be used in situations where the contribution of these components are either unknown or cannot be assumed

2.3.2 Objective Measures: Pedometer

Pedometers have gained widespread popularity in research and practice settings to quantify ambulation in terms of accumulated steps in free-living settings. Pedometers are small, inexpensive, battery operated devices worn at the waist that have the ability to measure ambulatory activity in terms of steps taken (and distance walked if stride length is available). The vertical forces of foot-strike cause movement of a spring-suspended lever arm to open and close an electrical circuit, which registers a “step”. In theory, step registration should reflect only the vertical forces of foot-strike and hence ambulatory activity. However, any vertical force through the hip area (e.g., sitting down hard onto a chair, riding on a bike or in a car over rough terrain) can also trigger the device.

Pedometers have demonstrated reasonable precision for use in research and clinical settings where walking is the primary type of activity. Moreover, their ease of administration makes them a practical assessment tool for individuals encompassing nearly all age groups. However, pedometers do not provide information relating to activity type, duration, or intensity. Therefore, accurate quantification of activity-related energy expenditure, time spent in type- or intensity-specific activities, and patterns of activity (e.g., short versus continuous bouts) cannot be assessed using the pedometer. Similar to other movement monitors, pedometers are unable to quantify upper body movements or to assess activity levels in individuals at slower gait speeds.
2.3.3 Physical Activity Assessment Issues in Women

It is well established that certain subgroups of the population (older adults and women) acquire most of their physical activity in lower intensity activities of which subjective measures tend to do a poor job assessing. Therefore, the supplemental use of objective measures may be required for a more accurate assessment of physical activity in these populations. This is particularly important when lower intensity activities comprise the bulk of energy expenditure.

2.4 POSTMENOPAUSAL WOMEN AND PHYSICAL ACTIVITY LEVELS

2.4.1 Relationship between Physical Activity Levels and CVD

With the mounting evidence against any cardio-protective benefits of hormone therapy, it is essential that other strategies be developed in order to prevent CVD among postmenopausal women. As mentioned previously, non-pharmacological strategies such as maintaining regular physical activity levels are particularly appealing. Unfortunately, older, postmenopausal women are among the least active subgroups in the U.S., with more than 41% of women in this age group reporting being physically inactive during their leisure time.

Over the past few decades, evidence has accumulated on the role of physical activity in the prevention and treatment of CVD. The evidence clearly suggests that individuals who participate in regular physical activity have a reduced risk of developing CVD. As a result,
physical inactivity has been identified as one of the major modifiable risk factors for CVD development due in part to the numerous physiological benefits.

In terms of cardiovascular benefits, physical activity improves myocardial contraction, decreases resting heart rate, and increases stroke volume both at rest and during exercise. Regular physical activity has been shown to improve endothelial function and flow-mediated dilation and increase coronary collateral artery formation. Physical activity also reduces platelet aggregation, which decreases the risk for clotting. Other adaptations that occur as a result of physical activity include the stimulation of lipid oxidation during activity and recovery and increases in lipoprotein lipase activity increases which in turn increases triglyceride clearance at rest and during activity. Regular physical activity levels also improves the sensitivity of liver, skeletal muscle, and adipose tissue to insulin. Physical activity is also indirectly protective against CVD development because it decreases blood pressure and obesity.

Prior studies demonstrating an inverse relationship between physical activity and CVD risk were mainly performed in men. The relationship between physical activity and CVD risk in women was inconclusive, with an assumed benefit extrapolated from what was found in men. The recent evidence for the relationship between physical activity levels and cardiovascular disease in postmenopausal women is presented in table 2.2 by study design.

Table 2-2: Recent evidence for the relationship between physical activity levels and cardiovascular disease development in postmenopausal women.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Association</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-Control</td>
<td>+/-0</td>
<td>Lemaitre&lt;sup&gt;152&lt;/sup&gt;; O’Conner&lt;sup&gt;153&lt;/sup&gt;</td>
</tr>
<tr>
<td>Prospective</td>
<td>+/-0/-0+/-0/+/-0/+/-0/+/-0/+/-</td>
<td>LaCroix&lt;sup&gt;44&lt;/sup&gt;; Lissner&lt;sup&gt;154&lt;/sup&gt;; Folsom&lt;sup&gt;45&lt;/sup&gt;; Kushi&lt;sup&gt;46&lt;/sup&gt;; Sesso&lt;sup&gt;47&lt;/sup&gt;; Manson&lt;sup&gt;48&lt;/sup&gt;; Lee&lt;sup&gt;49&lt;/sup&gt;; Manson&lt;sup&gt;47&lt;/sup&gt;; Owens&lt;sup&gt;50&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

+ indicates positive association; - indicates negative association; 0 indicates no association
Of the two case/control studies presented in table 2.2, one found a beneficial relationship between physical activity and cardiovascular outcome\textsuperscript{152} while another showed no relationship \textsuperscript{153}. Seven of the nine prospective studies presented in Table 2.2 found a beneficial relationship between physical activity and cardiovascular disease \textsuperscript{44-50}. The large number of studies suggesting an inverse relationship between physical activity levels and cardiovascular disease in postmenopausal women may be due to a number of factors, including the physical activity assessment tool that was used. The accuracy of the physical activity measure as other methodological factors will be described in detail in the following sections.

2.4.1.1 Accuracy of Physical Activity Assessment

All nine of the prospective studies presented in table 2.2 assessed leisure physical activity levels by subjective questionnaires \textsuperscript{43-50, 131, 153, 154} and did not rely on fitness measures that often reflect more vigorous types of activities. Three of the nine longitudinal studies examined if the protective effect of physical activity on CVD risk applies for moderate intensity activities that are common in women, such as walking. Data from these investigations indicate that moderate intensity activities are, in fact, associated with lower CVD rates in women \textsuperscript{48, 49, 155}, and that the benefits are similar for both moderate and vigorous activities \textsuperscript{48, 155}. There are no studies to date examining the relationship between CVD and lower intensity activities using objective monitoring.

2.4.1.2 Methodological Concerns

Although many studies presented in table 2.2 suggest an inverse relationship between physical activity and CVD, it should be noted that research in this area may have been affected by the possible misclassification of physical activity. Non-differential misclassification, a problem
intrinsic to the data collection methods, results from the degree of inaccuracy that characterizes how information was obtained in a particular study \textsuperscript{132}. For example, misclassification could occur in prospective studies if physical activity is measured only during study entry while current, not prior, activity levels would have been more protective against incident CVD that was assessed at the end of the study. Six of the nine prospective studies presented in table 2.2 assessed physical activity only at baseline \textsuperscript{43-46, 49, 155} and all had follow-up periods of 4 years or longer. Therefore, a major limitation to the findings of these six prospective studies is the possible misclassification of physical activity. Despite this potential limitation, only one of these six studies did not find an inverse association between physical activity and CVD \textsuperscript{43}.

Another consideration in prospective study designs is the possibility that the study cohort will not have enough incident cases of CVD during the study duration. A low CVD incidence affects the power to detect a statistically significant association. Five studies presented in table 2.2 had less than a 2\% incident rate for CVD [Folsom (1.2\%); Kushi (1.8\%); Manson (0.8\%); Lee (0.6\%); Manson (0.4\%)]\textsuperscript{45, 46, 48, 49, 155}. However, despite this low incidence rate, all five studies suggested an inverse relationship between physical activity levels and CVD development in women. This suggests that the beneficial effects of physical activity on CVD development may be mediated through positive changes to cardiovascular risk factors.

Another potentially important limitation of past studies on the role of physical activity in cardiovascular disease prevention in post-menopausal women is the treatment of hormone therapy. As mentioned in an earlier section, use of hormone therapy has been shown to affect the development of cardiovascular disease in postmenopausal women. However, five of the eleven studies presented in table 2.2 did not assess hormone therapy status and; therefore, did not adjust for this potentially confounding factor in their analyses \textsuperscript{44, 46, 152-154}.  

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Loss to follow-up presents another methodological limitation. One investigation reported a high percentage loss to follow-up. In the College Alumni Health Study, only 66% of the study cohort was followed successfully. This high loss to follow-up rate may explain why this study failed to find an association between physical activity and CVD.

A final methodological concern is that individuals who avoid physical activity may do so because of poor health or a functional limitation that is a result rather than a cause of his/her disease status. Individuals with sub-clinical disease may have limited function, which may limit physical activity. Sub-clinical disease has no recognizable clinical diagnosis and is distinct from a clinical disease with specific signs and symptoms. Therefore, low reported physical activity levels may serve as a marker of the disease process and not usual behavior. Likewise, individuals who participate in physical activity may also have other health-promoting lifestyle behaviors which may also affect CVD development.

### 2.4.2 Relationship between Physical Activity Levels and Lipids

Research investigating the relationship between physical activity and lipid levels in women has been inconclusive. The evidence for the relationship between lipids in postmenopausal women and physical activity is presented in table 2.3. Some prior cross-sectional studies have suggested that total cholesterol does not change with physical activity, while others have shown a decrease in total cholesterol levels. Prospective studies show the same inconsistencies with regards to total cholesterol levels, some have suggested no association, while others demonstrated an inverse relationship with physical activity. There has also been suggestion that physical activity is beneficially related to LDL levels, while others have shown no change. One cross-sectional study suggested a negative association, while another found no
association between physical activity levels and LDL cholesterol\textsuperscript{52}. Similar inconsistencies are obtained in longitudinal studies. An investigation by Binder et al.\textsuperscript{7}, suggested an inverse relationship, while others showed no association\textsuperscript{8, 53} between physical activity and LDL levels. With regards to triglycerides, some cross-sectional studies have suggested a decrease in triglyceride levels among postmenopausal women who participate in physical activity\textsuperscript{52, 54, 55}, while an investigation by Cauley et al.\textsuperscript{57} reported no change. Longitudinal studies investigating the relationship between physical activity and triglyceride levels among postmenopausal women have also be subject to the same discrepancies. Some investigations reported no association\textsuperscript{7, 8, 53, 58}, while one study reported an inverse relationship between physical activity and triglyceride levels\textsuperscript{19}. Many cross-sectional studies have suggested a beneficial effect of physical activity on HDL levels\textsuperscript{54-57}; however, prospective studies investigating this relationship have failed to validate this response\textsuperscript{7, 8, 19, 53, 58}.

Because of these uncertain findings, some have suggested that participation in physical activity may not be effective in postmenopausal women\textsuperscript{8}. However, as discussed in the following sections, the conflicting findings of prior studies may be related to the assessment tool used to measure physical activity as well as other methodological concerns, such as the selection of an appropriate study population and the possible interaction of hormone therapy in the relationship between physical activity and lipid levels.
Table 2-3: Evidence for the relationship between physical activity levels and lipids in postmenopausal women.

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Association</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>Cross-sectional</td>
<td>0/0/-/-</td>
</tr>
<tr>
<td></td>
<td>Prospective</td>
<td>-/-/0</td>
</tr>
<tr>
<td>Low Density Lipoprotein</td>
<td>Cross-sectional</td>
<td>0/-</td>
</tr>
<tr>
<td></td>
<td>Prospective</td>
<td>0/-/0</td>
</tr>
<tr>
<td>High Density Lipoprotein</td>
<td>Cross-sectional</td>
<td>+/-/0/+/-</td>
</tr>
<tr>
<td></td>
<td>Prospective</td>
<td>0/0/0/+0</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>Cross-sectional</td>
<td>0/-/-/-</td>
</tr>
<tr>
<td></td>
<td>Prospective</td>
<td>0/-0/0/0</td>
</tr>
</tbody>
</table>

+ indicates positive association; - indicates negative association; 0 indicates no association

2.4.2.1 Accuracy of Physical Activity Assessment

A number of investigations in the area of physical activity and lipids in postmenopausal women utilized measures of physical fitness as surrogates for population appropriate measurements of physical activity\(^7, 8, 53-55\). As mentioned previously, women tend to participate primarily in low to moderate intensity activities\(^157\). Therefore, fitness measures that reflect more vigorous activities may not be appropriate assessment tools to use in this population.

Surprisingly, the earliest three investigations included both subjective and objective measures of physical activity when examining this relationship in 229 postmenopausal women\(^56-58\). The combination of physical activity assessment measures provides information across the physical activity spectrum (Figure 2.1). In these studies, physical activity was measured subjectively using the Paffenbarger Harvard Alumni Survey and objectively using a Large-Scale Integrated (LSI) monitor. Both the cross-sectional\(^56, 57\) and longitudinal investigations\(^58\) suggested that physical activity as measured by objective measures of physical activity were not related to lipid levels. However, both cross-sectional studies\(^56, 57\) suggested a beneficial
relationship with HDL when physical activity was assessed subjectively. Despite the utilization of objective monitoring in these investigations, more work is needed using more recent and technologically advanced objective devices in a larger cohort of postmenopausal women.

2.4.2.2 Methodological Concerns

One methodological concern in the area of physical activity and lipids is the suggestion that individuals with elevated pre-exercise cholesterol levels respond more favorably to physical activity\textsuperscript{158}. Therefore, it may be unlikely that physical activity will make an impact on lipid levels that appear to be within normal limits. To date studies investigating the relationship between physical activity and lipids in postmenopausal women included only those with normal lipid profiles\textsuperscript{7, 8, 19, 52-58}.

Also, as mentioned previously, exogenous hormone therapy use alters the lipid profile of postmenopausal women. Past studies examining the relationship between physical activity and lipids have differed in their inclusion or exclusion of postmenopausal women on hormone therapy. Four of the ten studies presented in table 2.3 excluded hormone therapy users\textsuperscript{53, 56-58}, while another four investigations included both hormone therapy users and non-users\textsuperscript{8, 52, 54, 55}. Therefore, the inconclusive results demonstrated between physical activity and lipids in postmenopausal women may be partially explained by the differing inclusion/exclusion criteria used to define the study population.

NMR spectroscopy is a diagnostic test for the rapid and direct measurement of lipoprotein particle subclasses. Due to the novelty of this technology, there is currently limited information available on the relationship between physical activity and lipoprotein subclasses. The role of physical activity on specific lipoprotein subclasses, as well as those lipoprotein
subclasses that are thought to be related to CVD among postmenopausal women, has yet to be explored.

2.4.3 Relationship between Lifestyle Intervention and CVD Risk Factor Reduction

The combined benefit of physical activity, diet, and weight loss has been examined in randomized clinical trials testing the overall effect of a lifestyle based approach on CVD risk factor reduction and/or chronic disease prevention. Results from randomized clinical trials have demonstrated success in populations at risk for both type 2 diabetes\textsuperscript{25-28} and heart disease\textsuperscript{70}; however, few studies incorporating lifestyle have been done specifically in women at or after menopause.

The Women’s Healthy Lifestyle Project (WHLP) was developed in response to the previously mentioned prospective investigation known as the Healthy Women Study (HWS) (refer to section 2.1: Menopause and Cardiovascular Disease Risk). Again, the HWS was developed to examine the physiologic changes that take place during the menopausal transition. Findings from the HWS suggested that menopause is associated with weight gain and adverse CVD risk factor changes\textsuperscript{83}. Consequently, the WHLP was a 5-year randomized clinical trial designed to examine the effect of a behavioral based lifestyle intervention on weight gain and adverse changes to LDL-C that likely result during the menopausal transition\textsuperscript{71, 72}. At study entry, the WHLP population consisted of 535 healthy, pre-menopausal women who were randomly assigned to either a lifestyle intervention consisting of dietary and behavioral modification or to an assessment-only control group. Participants in the lifestyle intervention group were also given modest weight loss goals (5-15 lbs) to prevent weight gain above baseline
levels. Both groups attended follow-up clinic visits at 6, 18, 30, 42, and 54 months after randomization.

At the 54 month follow up visit, 56% of the entire study cohort were still menstruating regularly and considered pre-menopausal; 10% were peri-menopausal (having missed 3-11 consecutive periods), and 35% were post-menopausal (having missed 12 consecutive periods or having had a hysterectomy). Of those women who had become postmenopausal by 54 months, 56% of control and 61% of intervention participants reported HT use. Results from the WHLP demonstrated significant differences between randomized groups with regards to systolic and diastolic blood pressure, triglyceride, glucose, and insulin levels. In addition, the lifestyle intervention resulted in a significantly smaller increase in LDL-C levels over 54 months; this difference between randomized groups was similar among hormone users and non-users. Based on these promising findings, the investigators concluded that a lifestyle based approach can successfully attenuate the rise in LDL-C levels that results due to menopause.

The investigators from WHLP also explored the effectiveness of the lifestyle intervention to prevent weight gain. Again, the main weight goal of the intervention was to prevent weight gain above baseline levels. At 54 months, 55% of the participants randomized to receive the intervention were at or below baseline weight compared with only 26% of controls. More specifically, the mean weight change in the intervention group was 0.1 (5.2) kg below baseline levels compared with an average gain of 2.4 (4.9) kg that was observed in the assessment group. Not surprisingly, change in WC followed the same trend as weight change. With regards to behavioral modification, participants randomized to the intervention reported higher physical activity levels and consumed fewer calories and less fat than women in the assessment group.
Therefore, in addition to CVD risk factor reduction, the lifestyle intervention was also successful at preventing weight gain among women from peri- to post-menopause\textsuperscript{73}.

Unfortunately, little is known regarding the overall effectiveness of lifestyle modification for primary CVD prevention among postmenopausal women. In addition, findings from WHLP did not account for concurrent changes in HT status, an issue which has become particularly relevant in the post-WHI era. Therefore, the role of lifestyle on CVD risk factor reduction among postmenopausal women in various states of HT use has yet to be explored.

2.4.4 Relationship between Physical Activity, Walking Performance and Subclinical CVD Measures

As mentioned previously a large proportion of CVD related deaths occur in asymptomatic women. Specifically, approximately 2/3 of all sudden deaths attributable to CVD occur in women with no previous symptoms\textsuperscript{1,2}. Women differ from men with regards to both the clinical presentation of CVD and performance on standard diagnostic tests\textsuperscript{75}, making early detection among women a challenge. Therefore, in addition to prevention strategies, the development of tools that aid in the early detection of asymptomatic women who are at an increased risk of CVD has major public health implications.

Past epidemiological studies have shown that cardiovascular fitness, as measured by exercise capacity, is an independent predictor of cardiovascular events and death among asymptomatic women\textsuperscript{2,75,159,160}. Results from the St. James Women Take Heart Project study suggested that for each 1 MET increase in exercise capacity, there was a 17% reduction in all cause mortality among asymptomatic women\textsuperscript{75}. The prognostic value of measuring exercise capacity in women asymptomatic for CVD was confirmed in the Lipids Research Clinics
Based on these findings, the investigators concluded that the addition of a cardiorespiratory fitness measure to traditional risk factor assessment may be valuable for early detection, particularly among women with no apparent symptoms.

Maximal oxygen uptake (VO$_2$ max), the most accurate assessment of cardiovascular fitness, is typically estimated from a symptom limited treadmill or cycle ergometry based exercise stress test. However, VO$_2$ max protocols may not be practical in large epidemiological studies due to time constraints, staff burden and required medical oversight, high equipment costs, and safety concerns$^{76, 162}$. In instances where VO$_2$ max testing is not realistic, tests of walking endurance have been substituted for this gold standard measure to estimate fitness levels.

Walking endurance protocols were primarily developed to estimate exercise capacity in diseased and/or older populations$^{163}$. The walking endurance test, a 12 minute walking test, was introduced in 1968 as a submaximal, field test to estimate VO$_2$ max (based on achieved HR)$^{164}$. In 1982, Butland et al. found that decreasing the total duration of the test from 12 to 6 minutes, to make it more feasible in populations with chronic diseases, did not significantly reduce the utility of the test$^{165}$. As a result, the 6 minute walk test (6MWT) was used primarily in diseased populations who were not able to tolerate traditional VO$_2$ max protocols and/or long periods of exertion. Originally, the 6MWT was used to estimate fitness levels in individuals with chronic respiratory disorders$^{165-167}$. However, in the mid-1980’s, researchers reported the utility of this test to assess fitness levels in individuals with chronic heart failure$^{168, 169}$. Over time, the 6MWT protocol was applied to the elderly as a measure of functional status$^{170}$. Although the information obtained from the 6MWT provided information beyond that of traditional indicators, when validating this measure against the gold standard (treadmill or cycle ergometry based
exercise stress tests), it was determined that the relationship between peak O$_2$ consumption and distance walked during the 6MWT was not linear$^{169}$; therefore, the convergent validity of this instrument could not be assumed.

The long distance corridor walk (LDCW) is a slight modification of the 6MWT protocol, and was developed to extend the range of self paced walking tests in older adults$^{163}$. As opposed to measuring the distance covered over a predetermined duration (6 minutes), the LDCW protocol assesses the total time necessary to walk a 400 meter course. The LDCW was developed based on the thought that an individual may be more intrinsically motivated to complete a predetermined distance that can be visualized, in as little time as possible, thus providing a more maximal effort$^{162}$. A 2001 investigation directly compared the overall work effort, as indicated by walking speed, and ending heart rate (HR) and systolic blood pressure (SBP), from the 6MWT and LDCW, and results confirmed that a target distance encouraged individuals to walk closer to their maximal effort when compared to a time dependent protocol$^{162}$.

The LDCW has been utilized in well-functioning healthy older individuals with promising results. Results from a cross-sectional investigation using the Health, Aging, and Body Composition study (Health ABC) suggested that walking performance was influenced by both clinical and subclinical diseases and was strongly related to anthropometric measures and self reported physical activity levels. Results from the follow-up Health ABC investigation suggested that exclusion or inability to complete the LDCW protocol was associated with an increased risk of mortality, incident CVD, and mobility limitation$^{171}$. For those that completed the protocol, each additional minute of walk time was associated with a 29% higher rate of mortality, a 20% higher rate of incident CVD, and 52% higher rates of mobility limitation and
These findings suggest that measured parameters from the LDCW, particularly walk time, are useful for estimating risk of mortality and/or disease among older adults. In addition to risk assessment, the use of the LDCW to estimate physical fitness levels was investigated. The relationship between walk time from the LDCW and peak VO\(_2\) measures obtained during a treadmill based protocol (modified Balke) were examined in 102 participants, aged 60 to 91, from the Baltimore Longitudinal Study of Aging (BLSA). The correlation between walk time and peak VO\(_2\) was -0.79, indicating a strong relationship between the measured parameters. Therefore, in contrast to the 6MWT, the convergent validity of the LDCW to estimate fitness levels among older individuals can be assumed.

It is fairly well established in the literature that the LDCW is a low cost alternative for estimating cardiovascular fitness levels and is useful for assessing mortality and incident disease risk in older individuals; however, little is known regarding the applicability of this test in middle-aged, postmenopausal women.

### 2.5 CONCLUSION

The literature provides strong evidence for the 1) association between physical activity and lipid levels, 2) positive role of lifestyle based interventions for CVD risk factor reduction and primary CVD prevention, and 3) usefulness of the LDCW to ascertain CVD risk. However, an examination of this literature also exposes the fact that several studies in this field have limitations in their design that can be addressed in future research. This project will address these shortcomings by using 1) both subjective and objective physical activity assessment tools, 2) direct measure of lipoprotein particle subclasses, 3) subclinical CVD measures, and 4)
measured parameters from the LDCW. The project will also examine the added influence of current and/or change in HT use on these relationships. With these improvements, we expect that this project will make a significant contribution to the existing literature.

2.5.1 Objectives of the Project

The proposed investigation will examine the 1) relationship between leisure physical activity, lipids, and lipoprotein subclass levels and investigate how current HT use may influence these associations, 2) effectiveness of a lifestyle intervention to attenuate unfavorable changes to CVD risk factors that result from HT discontinuation, and 3) associations between walking performance, physical activity levels, and subclinical CVD measures in 508 postmenopausal women, aged 52-62 years. Specifically, the study meets the following objectives:

**Paper 1**: Examine the cross-sectional relationship between physical activity levels and lipoprotein subclasses by hormone therapy status at baseline.

a. It is hypothesized that leisure physical activity will be beneficially related to some of the lipoprotein sub-classes in postmenopausal women; however, there will be a few lipoprotein subclasses in which physical activity is only significantly related in women not taking hormone therapy.

**Paper 2**: To determine if a lifestyle intervention promoting weight and waist circumference reduction through beneficial physical activity and dietary practices can attenuate unfavorable CVD risk factor changes that are likely to occur as postmenopausal women discontinue hormone therapy (HT) use.

a. It is hypothesized that discontinuation of hormone therapy has negative consequences on many CVD risk factors.
b. It is further hypothesized that a lifestyle intervention will attenuate negative consequences of discontinuing hormone therapy with regards to many CVD risk factors.

**Paper 3:** To determine the utility of the LDCW as a measure of health status in middle-aged, postmenopausal women.

a. Walking performance, more specifically walk time, will be significantly related to demographic factors, anthropometric measures, subjective and objective measures of physical activity, and CVD risk factors in postmenopausal women.
3 METHODS

3.1 BRIEF OVERVIEW OF THE WOMAN CLINICAL TRIAL

The WOMAN Study is a five-year randomized clinical trial designed to test whether an aggressive non-pharmacological intervention among postmenopausal women currently or previously on HT would modify or reduce measures of subclinical cardiovascular disease. Eligibility criteria for enrollment into the study included: age 52-62 years, waist circumference ≥ 80 centimeters (cm), body mass index between 25-39.9 kilograms per meters squared (kg/m²), not currently taking lipid lowering drugs, having a low density lipoprotein (LDL-C) level between 100-160 milligrams per deciliter (mg/dL), no physical limitation that would preclude walking, no known diabetes, and no diagnosed psychotic disorder and depression. Eligible WOMAN study participants (n=508) were randomized into one of two groups: lifestyle change (intervention) (n=253) and health education control (n=255).

Table 3.1 illustrates the measures central to this proposed plan and the number of WOMAN study participants that completed each measure. Those that completed the clinic visit also completed all measurements that were obtained during that visit including demographics, medication inventory (hormone therapy (HT) and other medication use), anthropometric measures (BMI and waist circumference), blood pressure, and fasting blood draw (plasma cholesterol, insulin, and glucose). It should be noted that the WOMAN study cohort represents a
higher than normal risk for CVD based on higher waist circumference and BMI criteria at entry. Changes in HT recommendations\textsuperscript{13} that were made during mid-recruitment resulted in a cohort of postmenopausal women with varied HT status. Therefore, the HT component of the WOMAN study was not randomized. Additionally, these changes in recommendations resulted in a number of women changing HT status as they progressed through the first 18 months of the 5-year long study.

Table 3-1: Time Line for WOMAN Study Measurements through the 18 Month Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Baseline/Screening Visit</th>
<th>6-Month Follow-up Visit</th>
<th>18-Month Follow-up Visit</th>
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<tr>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
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<tr>
<td></td>
<td>(n=508)</td>
<td>(n=485)</td>
<td>(n=455)</td>
</tr>
<tr>
<td><strong>Completed Clinic Visit</strong></td>
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</tr>
<tr>
<td>(including demographic survey, medication inventory, anthropometric measures, blood pressure, and fasting blood draw)</td>
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<tr>
<td><strong>Physical Activity Measures</strong></td>
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<tr>
<td>Past Year MAQ</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td>(n=504)</td>
<td>(n=484)</td>
<td>(n=455)</td>
</tr>
<tr>
<td>Past Week MAQ</td>
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<tr>
<td></td>
<td>(n=506)</td>
<td>(n=467)</td>
<td>(n=440)</td>
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<tr>
<td>Pedometer</td>
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<td>x</td>
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<td>(n=173)</td>
<td>(n=323)</td>
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<td>Coronary Artery Calcification (EBCT)</td>
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<tr>
<td>Carotid Ultrasound</td>
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<td>(n=503)</td>
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</table>
3.2. MEASURES

3.2.1. Physical Activity Measures

3.1.1.1 Past Year Modifiable Activity Questionnaire (MAQ)

Physical activity was measured using the MAQ, an interviewer administered, past-year questionnaire\cite{144}. The MAQ has been shown to be both reliable\cite{144,174} and valid\cite{144,174,175} and has been used to assess physical activity levels in over 200 studies consisting of populations from all over the world. This questionnaire assesses current leisure and occupational activities, as well as extreme levels of inactivity due to disability. Study participants were asked to report if they participated in specific activities, such as walking for exercise, at least 10 times over the past year (12 months). For those that participated in a specific activity, they were asked which months they had participated in that specific activity over the past year and then estimated the number of times each month and length of time that they spent doing the specific activity. Physical activity levels were calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the metabolic equivalent (MET) of that activity and summed for all activities performed. One MET represents the energy expenditure for an individual at rest, whereas a 10-MET activity requires 10 times the resting energy expenditure\cite{176}. Physical activity data were expressed as metabolic equivalent hours per week (MET hr-wk).

For occupational activity, individuals were asked to list all jobs held during the past 12 months. For each job entry, data were collected for minutes per day walking or cycling to work, as well as the number of months per year, days per week, and hours per day spent working in that job. Job activity was determined by the number of hours spent sitting at work and the most
frequent activities performed when not sitting. Housewives, unemployed, physically challenged, and retired individuals were questioned about activities during a normal “40 hour work week”.

Estimates of leisure and occupational activity were calculated separately as hours per week (h wk) averaged over the past year. Total physical activity was the combination of leisure and occupational activity averaged over the past year.

3.1.1.2 Past Week Modifiable Activity Questionnaire (MAQ)

Physical activity was also assessed using a past week version of the MAQ. This questionnaire measures participation in leisure activities performed over the past 7 days. Study participants were given the past week MAQ during the eligibility visit and were asked to record leisure activities for the 7 days prior to their clinic assessment. Past week leisure physical activity levels were calculated similar to that used for the leisure section of the past year MAQ.

3.1.1.3 Pedometer

Physical activity was measured using the Accusplit Eagle (AE120) pedometer. At baseline, pedometer data was collected on a subgroup of women entering the study; however, was available to all participants at the 18 month clinic visit. The participant was instructed to wear the pedometer clipped to her waistband over the dominant hip for one week, and at the end of each day to record the number of steps taken in a diary. At the end of the week the participant returned the activity diary to the investigator. The number of steps recorded in the diary from the pedometer was averaged for the week to obtain a seven-day average of the number of steps taken per day.
3.1.2 Completed Clinic Visit

The proposed investigation examines the relationship between physical activity and cardiovascular risk factors in postmenopausal women during the first 18 months of the 5 year long study. The completed baseline and 18 month clinic visits will be critical for proposed examination. All relevant demographic and clinical measures (ie. anthropometrics, fasting blood draw) were collected during these time points.

3.1.3 Lipoprotein Subclasses

Participant blood samples were drawn after a 12 hour fast. Lipoprotein subclasses were measured by nuclear magnetic resonance (NMR) spectroscopy (Liposcience Inc., Raleigh, NC), as previously described \textsuperscript{177}. In brief, the lipoprotein subclasses were quantified using characteristic signals, which differ in frequency and shape depending on the diameter of the lipoprotein particle, as a basis for quantification. Each signal was derived from the total number of terminal methyl groups on the lipids contained within the particle core and in the surface shell. The intensity of each signal was proportional to the quantity of the subclass and was multiplied by a standard lipid amount to provide results in mg/dL of cholesterol for low density lipoprotein (LDL) and high density lipoprotein (HDL) and mg/dL of triglyceride for very low density lipoprotein (VLDL). The lipoprotein subclasses were categorized as large (60- to 200-nm), medium (35- to 60-nm), and small (27- to 35-nm) VLDL; IDL (23- to 27-nm), large (21.3- to 23.0-nm), medium (19.8- to 21.2-nm), small (18.3- to19.7-nm), and very small ($\leq$ 18.2-nm)
LDL; and large (8.8- to 13-nm), medium (8.2- to 8.8-nm), and small (7.3- to 8.2-nm) HDL. Particle concentrations (nmol/L for VLDL and LDL; μmol/L for HDL) were calculated for each subclass standard by measuring the total concentration of core lipid and dividing the volume occupied by these lipids by the core volume per particle calculated from the diameter of that particle 178, 179.

3.1.4 Long Distance Corridor Walk

The LDCW consisted of 400 meter walk along a course consisting of 10 laps along a hallway with cones set 20 meters apart (40 meters per lap). Participants were instructed to walk “at a pace that you can maintain for the full 10 laps.” Standard encouragement by a trained clinician was given at each lap. Heart rate was monitored with a Polar Pacer hear monitor (Model 60905; Woodbury, NY). Persons with elevated blood pressure (BP ≥200/110), resting heart rate (>110 or <40), recent exacerbation of chest pain, shortness of breath, or reporting a recent cardiac event or procedure were excluded for safety reasons. The LDCW was stopped if the participant’s heart rate exceeded 135 beats per minute (bpm) or if a participant reported chest pain or dyspnea during the test. Heart rate (HR) was recorded at rest before starting the walk, at completion, and at recovery 2 minutes later. Systolic blood pressure (SBP) was measured while seated prior to the walk and while standing at test completion. Based on these measures, cardiovascular response variables were generated. HR and SBP response were calculated by subtracting the resting values from those obtained immediately following completion. HR recovery was calculated by subtracting the HR obtained 2 minutes after LDCW completion from the value measured at completion.
3.1.5 Measures of Subclinical Disease

3.1.5.1 Electron Beam Computed Tomography (EBCT)

The participant was positioned supine on the table with the head toward the gantry; a bolster pillow was placed under the knees for comfort. After careful skin preparation, electrodes were placed and an optimum EKG tracing was obtained. The participant’s body was next positioned within the gantry with arms over head and resting on the arm rests. The laser-guided light was positioned over the participant’s xiphoid process. A second laser-guided light was used to adjust the table height so the participant was centered within the gantry. The participants had to hold their breath during the scanning. Each time the scanner was operated, they were instructed to take a breath in, let it out, take a second breath, let it out, and take a third breath, and hold it. The first scan was a preview scan, which served the purpose of calibrating to chest size of the given participant. The second scan imaged the entire heart, with cross-sectional images at every 3 mm. The pictures were taken during the diastolic phase of the cardiac cycle, one image during each heart beat. We obtained 30-40 contiguous 3mm thick transverse images from the level of the aortic root to the apex of the heart. Images were obtained during maximal breath holding using EKG triggering so that each 100m second exposure was obtained during the same phase of the cardiac cycle, 60% of the RR interval.

All EBCT studies were read at the University of Pittsburgh. Readings of coronary calcification were done using a DICOM workstation and software by Accuimage (San Francisco, CA). This software program implements the widely accepted Agaston scoring method. Coronary artery calcium was considered to be present when 3 contiguous pixels greater than 130 Hounsfield units were detected overlying the vessels of interest. Scoring results in a total calcium score as well as a total number of calcifications.
3.1.5.2 Carotid Ultrasound

The scanning procedure results in three primary carotid disease measures: average wall (intima-media) thickness, a measure of degree of focal plaque called the plaque index, and the ICA/CCA velocity ratio, a determination of whether or not plaque is interfering with blood flow in the internal carotid artery. Carotid ultrasound measurements were obtained using a Toshiba SSA-270A scanner in Pittsburgh, PA. Briefly, detailed B-mode images of the right and left common carotid artery, carotid bifurcation and the first centimeter of the internal carotid were obtained. Selected images were digitalized for later measurement of the intima-media thickness by central readers in Pittsburgh. After imaging, the sonographer obtained Doppler measures of blood flow velocity at mid common (2 cm proximal to the carotid bulb) and in the internal carotid at the point of the highest velocity distal to the flow divider. These were used to calculate the degree to which plaque may be interfering with blood flow. Plaque was defined as a distant focal area protruding into the vessel lumen. Plaque was assessed in 4 areas: proximal common, distal common, carotid bulb, and internal carotid. For each segment, the degree of plaque was graded using the following criteria: Grade 0 = no observable plaque; grade 1 = one small plaque (less than 30% of the vessel diameter); grade 2 = one medium plaque (between 30 and 50% of the vessel diameter) or multiple small plaques; grade 3 = one large plaque (greater than 50% of the vessel diameter) or multiple plaques with at least one medium plaque. The grades were then summed to create a plaque index, a measure of the extent of eccentric plaque.

Stiffness of the aorta was measured using the gold standard, carotid-femoral (or aortic) pulse wave velocity (aPWV), as previously described in detail\textsuperscript{181, 182}. Briefly, for each participant, 20 seconds of carotid and femoral pulse waveforms were collected simultaneously with non-directional Doppler probes and recorded to data files. Files were “scored” using
software developed by the Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging. For each file, the trained reader selected all clear waveforms for averaging into composite carotid and femoral waveforms, to determine the “foot” (or upstroke) of each. The transit time of the pulse wave was calculated as the foot-to-foot delay between the averaged carotid and femoral waveforms. The distance traveled by the pulse waveform between the carotid and femoral measurement sites was measured manually with a metal tape measure, above the surface of the participant’s torso. Aortic pulse wave velocity was calculated by dividing the distance traveled by the time differential between the two waveforms and expressed as distance/transit time (cm/sec). Results from all usable data collection runs (n = 3) for each participant are averaged. In our lab this measure has been demonstrated to have good reproducibility with an intraclass correlation of 0.72-0.83\(^{181}\).

### 3.3. STATISTICAL ANALYSIS

Briefly described below are the analytical procedures for papers 1-3. The specific methodologies are described in greater detail within the context of each respective paper.

Paper #1: The primary hypothesis of paper #1 was to determine if leisure physical activity is beneficially related to many of the lipoprotein sub-classes in postmenopausal women. A secondary hypothesis was that there are some lipoprotein subclasses in which physical activity is only significantly related in women not taking hormone therapy. To test the primary and secondary hypotheses, the following statistical procedures were performed.

Descriptive statistics were used to describe demographic, anthropometric measures, physical activity, and lipoprotein subclass levels in the entire cohort and stratified by HT use.
All variables were assessed for normality. Normally distributed variables were reported as mean ± standard deviation; not normally distributed variables were reported as median with 25th and 75th percentiles. Depending upon the characteristics of the variable, t-tests, Wilcoxon Rank Sum, or Chi Square ($\chi^2$) tests were used to compare HT users and non-users.

For each lipoprotein subclass, we evaluated four multivariate linear regression models. The first model examined the association between physical activity and lipoprotein subclasses after controlling for age and saturated fat/cholesterol intake. The second model added BMI and the third model added HT status as covariates. The fourth model evaluated the addition of a physical activity*HT interaction term to these models. For graphic representation, we evaluated the lipoprotein subclass levels across physical activity quartiles. Jonckheere-Terpstra tests were also used to estimate linear trends in mean lipoprotein subclass levels across physical activity quartiles stratified by HT status.

Paper #2: The primary hypothesis of paper #2 was that discontinuing hormone therapy may increase certain CVD risk factors and that a lifestyle intervention can attenuate the effect of discontinuing HT on CVD risk factors. To test the primary hypothesis, the following statistical procedures were performed.

The study population for this analysis consisted of a subgroup of the WOMAN study participants who were on HT at study entry. Descriptive statistics were used to describe baseline anthropometric measures, leisure physical activity levels, and CVD risk factor levels by HT group (those that continued verses discontinued use at the 18 month follow-up visit). Normally distributed variables were reported as mean ± standard deviation; non-normally distributed variables were reported as median with 25th and 75th percentiles. Depending upon the
characteristics of the variable, t-tests or Wilcoxon Rank Sum tests were used to compare baseline CVD risk factor values between HT continuers and HT discontinuers.

The 18 month change in anthropometric, physical activity, and CVD risk factor variables over time were calculated as the difference in values between the 18 month follow-up and baseline. Change variables were reported and compared between HT continuers and HT discontinuers, stratified by randomized group assignment using t-tests or Wilcoxon Rank Sum tests. CVD risk factor change was also reported and compared between randomized groups, stratified by HT status at the 18 month clinic visit.

Further post-hoc analyses were conducted to determine the independent effect of healthy lifestyle behaviors that were promoted in the lifestyle intervention on CVD risk factor reduction using multivariate linear regression models. The multivariate model examined the longitudinal relationship between CVD risk factor and change in leisure physical activity, and saturated fat/cholesterol intake, after adjusting for HT status at 18 months and baseline levels of leisure physical activity, saturated fat/cholesterol intake, and relevant CVD risk factor.

Paper #3: The primary hypothesis of paper #3 was that walking performance obtained from the LDCW was related to physical activity levels and measures of subclinical CVD among postmenopausal women. A secondary hypothesis was that the cardiovascular response measures obtained from the LDCW was related to physical activity levels and measures of subclinical CVD. To test the primary and secondary hypotheses, the following statistical procedures were performed.

Univariate analyses were conducted on measured parameters from the LDCW, demographics, physical activity levels, and measures of subclinical CVD. Normally distributed variables were reported as mean ± standard deviation, non-normally distributed variables were
reported as median with 25th and 75th percentile, and proportions were noted for categorical variables. Spearman rank order correlation coefficients were used to assess the bivariate associations between walk time and CV response measures from the LDCW, demographics, physical activity levels, and CVD risk factors and partial Spearman rank order correlations were used to examine these relationships adjusted for age and BMI. Descriptive statistics were used to illustrate demographics, physical activity levels, and CVD risk factors across quartiles of LDCW time. Depending upon the characteristics of the variable, ANOVA, Kruskal-Wallis, or Chi Square Test of Proportions was used to compare demographic factors, physical activity levels, clinical and subclinical CVD measures across quartiles of LDCW time in those who completed the 400-meter walk. Jonckheere-Terpstra tests were used estimate the linear trend in continuous variables and Cochran-Armitage Trend test were used to determine linear trend for categorical variables. To adjust for the high number of planned comparisons, a p value of <0.002 was used to denote statistical significance using the Bonferonni correction method.

3.4. CONCLUSION

Results from the proposed three papers will add to the growing body of evidence regarding strategies for primary prevention of CVD in postmenopausal women. The proposed investigation will add to the literature through the use of 1) both subjective and objective physical activity assessment measures, 2) direct measure of lipoprotein particle subclasses, 3) subclinical measures of CVD, and 4) measured parameters from the LDCW. Finally, the WOMAN study participants represent a unique cohort who were directly affected by the results
from the WHI\textsuperscript{13}. The change in HT recommendations provides the opportunity to examine the health impact of the widespread discontinuation of HT.

With this information we will be able to: 1) examine the cross-sectional relationship between physical activity levels and lipoprotein subclasses by HT status at baseline, 2) determine if a lifestyle intervention can attenuate unfavorable CVD risk factor changes that are likely to result from HT discontinuation, and 3) determine the construct validity of the LDCW in postmenopausal women.
THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND LIPOPROTEIN SUB-CLASS LEVELS IN POST-MENOPAUSAL WOMEN: THE INFLUENCE OF HORMONE THERAPY

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Kelley K. Pettee MS\textsuperscript{1}, Andrea M. Kriska PhD\textsuperscript{1}, B. Delia Johnson PhD\textsuperscript{1}, Molly B. Conroy\textsuperscript{1,2} MD, Trevor J. Orchard\textsuperscript{1} MD, Rachel H. Mackey\textsuperscript{1}, Lewis H. Kuller\textsuperscript{1} MD

\textsuperscript{1} Department of Epidemiology
\textsuperscript{2} Division of General Internal Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA
4.1 ABSTRACT

OBJECTIVE: To determine if the association between physical activity and lipids and lipoprotein subclasses in postmenopausal women varies by hormone therapy (HT) use.

DESIGN: The cross-sectional relationship between physical activity and lipid and lipoprotein subclass relationship was examined prior to group randomization in 485 postmenopausal [mean age 56.9 (2.9 years)] Caucasian and African-American women from the Woman On the Move through Activity and Nutrition (WOMAN) Study. The WOMAN study is a randomized clinical trial designed to test whether a lifestyle intervention will reduce subclinical cardiovascular disease measures. RESULTS: HT users (n=286) were significantly (p<0.05) younger, less likely to be African American, reported higher levels of physical activity, large VLDL particles (VLDL-P), and medium HDL particles (HDL-P), had a larger mean HDL particle size, and lower levels of total cholesterol, LDL cholesterol (LDL-C), small HDL-P, and small VLDL-P than non users (n=196). Physical activity was significantly associated with favorable lipoprotein and lipid levels, regardless of HT use. Some relationships were found to vary significantly by HT use. In non-users, mean HDL and LDL particle size was significantly smaller and total and small LDL particles (LDL-P) were significantly lower as activity increased. These relationships were not found in HT users. CONCLUSIONS: Physical activity was significantly related to some lipoprotein subclasses regardless of HT. However, several key lipoprotein subclasses were associated with higher levels of activity only among non-HT users.

Key Words: physical activity, lipids, lipoprotein subclasses, hormone therapy, postmenopause
4.2 INTRODUCTION

Currently in the United States, cardiovascular disease (CVD) is the leading cause of death among older women (1). The cessation of ovarian function and the subsequent decrease in endogenous sex steroid hormone levels that occur as a result of the menopausal transition are associated with adverse lipid changes, which are thought to be largely responsible for the rising prevalence of CVD in postmenopausal women (2, 3). The menopausal transition is associated with increases in both total cholesterol and LDL cholesterol (LDL-C) and a decrease in HDL cholesterol (HDL-C) (4, 5).

Among postmenopausal women, hormone therapy (HT) has been shown to lower total and LDL-C and increase HDL-C (2). As a result, HT was widely prescribed lipid lowering and general CVD prevention in addition to menopausal symptom relief (6, 7). However, recent evidence from randomized clinical trials (8-11) has failed to confirm the cardio-protective benefits of HT that were suggested from earlier, observational studies. Since these results have been published, there have been significant changes in clinical practice regarding the prescription of HT. HT is no longer prescribed for lipid lowering and/or general CVD prevention. This clinical trend, combined with other documented risks of HT has caused prescription rates of HT use to plummet (12). This creates the need for other strategies to be employed to favorably alter the lipid profile and decrease CVD risk in postmenopausal women.

CVD risk attributable to dyslipidemia may be better quantified using specific lipoprotein subclass measurement as opposed to conventional methods (13). There is increasing evidence that subclasses of LDL, HDL, and VLDL (differentiated by particle size or density) may differentially predict CVD. Among postmenopausal women, the measurement of LDL subclasses may be particularly important. Past studies have suggested that smaller mean LDL
particle size, higher levels of total LDL particles (LDL-P) (14), and higher levels of small LDL-P are associated with incident CVD (15) and subclinical atherosclerosis (16) among postmenopausal women. Evidence also suggests that the associations between these key LDL lipoprotein subclasses and measures of subclinical CVD remain regardless of hormone therapy status (17). HDL subclass measures [e.g. larger mean HDL particle size or higher large HDL particles (HDL-P)] have also been shown to have incremental predictive value for coronary artery disease (CAD) and incident coronary heart disease (CHD) (18-20).

Past research does not clearly define the relationship between physical activity and the overall lipid profile in postmenopausal women (21). The purpose of the current investigation is to clarify these associations by including both specific lipoprotein subclass measures, as well as traditional lipid measures. A secondary aim is to examine how HT may modify the relationship between leisure physical activity and lipoprotein subclass and lipid levels in postmenopausal women.

4.3 METHODS

The Women On the Move through Activity and Nutrition (WOMAN) Study is a five year primary CVD prevention randomized clinical trial, designed to test whether an aggressive non-pharmacological lifestyle intervention among postmenopausal women will reduce measures of subclinical CVD. This study provides a unique opportunity to explore the relationship between physical activity, lipids, and nuclear magnetic resonance (NMR) spectroscopy-determined lipoprotein subclasses in postmenopausal women currently using and not using HT.
4.3.1 Study Population

Five hundred and eight postmenopausal women were recruited for the WOMAN study, primarily through direct mailing from selected zip codes in Allegheny County, Pennsylvania from April 2002 to October 2003. Eligibility criteria for enrollment into the study included waist circumference $\geq 80$ centimeters (cm), body mass index (BMI) between 25 – 39.9 kilograms per meters squared ($\text{kg/m}^2$), not currently taking lipid lowering drugs and having a low density lipoprotein cholesterol (LDL-C) level between 100 - 160 milligrams per deciliter (mg/dL), no physical limitations that would preclude walking, no known diabetes, and no diagnosed psychotic disorder or depression. All participants provided written informed consent and all protocols were approved by the institutional review board at the University of Pittsburgh. Results were based on data collected prior to randomization at the baseline clinic visit (2002-2003).

4.3.2 Physical Activity

Physical activity was measured using the Modifiable Activity Questionnaire (MAQ), an interviewer-administered, past-year questionnaire (22). This questionnaire assesses current leisure and occupational activities, as well as extreme levels of inactivity due to disability. Physical activity levels were calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the metabolic equivalent (MET) of that activity and summed for all activities performed. For the purposes of this investigation, only leisure physical activity estimates were used. Leisure physical activity data were expressed as
metabolic equivalent hours per week (MET hr-wk). The MAQ has been shown to be both reliable (22, 23) and valid (22-24).

4.3.3 Hormone Therapy Status

HT status was obtained through self-report in addition to a medication inventory that was completed at the baseline clinic visit. Participants were classified as being either current HT users or non-users.

4.3.4 Lipid and Lipoprotein Subclass Measures

Total cholesterol, HDL-C, and triglycerides were determined by conventional methods from fasting (12 hour) blood samples. LDL-C was estimated by the Friedewald equation. Lipoprotein subclass particle concentrations and mean particle diameters were measured using an automated nuclear magnetic resonance (NMR) spectroscopic assay (LipoScience, Inc., NC) as previously described (25) in detail. Unlike conventional lipid measures, which quantify lipoproteins according to the amounts of lipid (cholesterol or triglyceride) carried by all of the particles in the major class, the NMR spectroscopy assay determines concentrations of lipoprotein particles according to particle size (diameter). Results are then grouped into small, medium, and large subclasses for HDL-P and VLDL-P. For LDL, the particle concentrations are reported for small and large LDL-P in addition to intermediate density lipoprotein particles (IDL-P). Subclasses are summed to provide total LDL-P, HDL-P, and VLDL-P. Mean LDL and HDL particle sizes are calculated as weighted-averages (i.e. the diameter of each subclass multiplied by its relative mass percentage).
4.3.5 Other Measures

Demographic factors, such as age, saturated fat and cholesterol intake (fat intake index), body mass index (BMI) were considered confounding variables. BMI was calculated from height and weight measured with a stadiometer and calibrated balance beam scale, respectively. Fat intake index was assessed using the Connor Diet Habit Survey, which has been shown to be both a reliable and valid measure for the rapid assessment of eating habits and diet composition (26).

4.3.6 Analytic Procedures

Descriptive statistics were used to describe demographic, anthropometric measures, physical activity, and lipoprotein subclass levels in the entire cohort and stratified by HT use. Normally distributed variables were reported as mean ± standard deviation; non-normally distributed variables were reported as median with 25th and 75th percentiles. Depending upon the characteristics of the variable, t-tests, Wilcoxon Rank Sum, or Chi Square ($\chi^2$) tests were used to compare HT users and non-users.

For each lipoprotein subclass, we evaluated four multivariate linear regression models. The first model examined the association between physical activity and lipoprotein subclasses after controlling for age and saturated fat/cholesterol intake. The second model added BMI. The third model added HT status. The fourth model evaluated the addition of a physical activity*HT interaction term to the models. For graphic representation, we evaluated the lipoprotein subclass levels across leisure physical activity quartiles by HT status. Activity quartiles represented the distribution of leisure physical activity levels reported in the WOMAN study. Jonckheere-
Terpstra tests were used to estimate the linear trend in mean lipoprotein subclass levels across physical activity quartiles by HT status.

### 4.4 RESULTS

Twenty-six women (5.1%) had incomplete data and were excluded from these analyses. Of the remaining 482 WOMAN study participants with complete data, 59.3% (n = 286) reported taking HT and 40.7% (n = 196) of the women reported not taking HT at the baseline assessment. Of those women who reported taking HT at baseline, 120 (42% of HT users) women took estrogen therapy (ET), while the remaining 166 (58% of HT users) took estrogen plus progestogen therapy (EPT). The mean age of the participants was 56.9 ± 2.9 years, and 11.6% were African American (Table 4.1). Study participants had a mean BMI of 30.7 ± 3.8 kg/m² and waist circumference of 105.7 ± 11.2 centimeters. Only 6.2% of women reported being current smokers. The median physical activity levels reported in the WOMAN study cohort at baseline were similar to those recommended by the Surgeon General for physical activity and health.

Compared to non users, HT users were significantly younger (p<0.05), were less likely to be African American, and reported higher levels of physical activity (Table 4.1). In addition, HT users had significantly higher large VLDL particles (VLDL-P), and medium HDL-P levels. HT users also had a significantly larger mean HDL particle size, and lower levels of total cholesterol, LDL-C, small HDL-P and small VLDL-P than non-users. No additional significant differences were found between HT groups for the remaining lipid or lipoprotein levels (Table 4.1).

In separate multivariable linear regression models in the entire cohort, after adjustment for age and fat intake index, leisure physical activity was significantly related to higher levels of
HDL-C (p=0.001) and large HDL-P (p=0.02) and lower total and medium VLDL-P (p=0.001; p=0.003 respectively), and triglycerides (p=0.03). However, for the entire cohort, after adjustment for age and fat intake, leisure physical activity was not significantly related to mean HDL or LDL particle size, total, small LDL-P, total cholesterol, total, medium, or small HDL-P, IDL-P, LDL-C, large LDL-P, or large or small VLDL-P (data not shown).

When BMI was added to the model results were similar. BMI was a significant covariate in most models (p<0.01 to <0.001). Although BMI attenuated the relationship between leisure physical activity and HDL-C, large HDL-P, and triglycerides, physical activity remained a statistically significant covariate for each of these lipid and lipoprotein subclass variables. It should be noted that results were similar when waist circumference was substituted in the model for BMI (data not shown).

Similarly when HT was added to the multivariate model, results were similar. Activity levels were significantly related to higher levels of HDL-C (p=0.01) and large HDL-P (p=0.008) and lower levels of total and medium VLDL-P (p=0.003, p=0.005 respectively), and triglycerides (p=0.006), (Table 4.2). Physical activity was not significantly related to mean HDL or LDL particle size, total, small LDL-P, total cholesterol, total, medium, or small HDL-P, IDL-P, LDL-C, large LDL-P, or large or small VLDL-P (data not shown). HT was a significant covariate only for lower HDL-C levels (p<0.01), but not for other lipoproteins. Moderate alcohol intake was also considered as a possible confounding factor. However, the addition of this factor to the models did not significantly change the results; therefore, it was not included in final multivariate models.

After adjusting for potential confounders, the physical activity*HT interaction term was only statistically significant for mean HDL and LDL particle size, total and small LDL-P.
Therefore, we further evaluated the relationship between leisure physical activity and those four key lipoprotein subclass measures after stratifying by HT use (Figure 4.1). Among HT users, there was no significant association between physical activity and these lipoprotein subclasses (Figure 1). In contrast, among HT non-users, higher leisure physical activity was significantly associated with lower total and small LDL-P and larger mean LDL and HDL particle sizes. Furthermore, among HT non-users, these relationships remained statistically significant after adjustment for age, body mass index, and saturated fat/cholesterol intake (Table 4.3).

4.5 DISCUSSION

The present investigation was the first to investigate the associations between lipids, physical activity, and HT using specific lipoprotein subclasses. In this large cohort of overweight postmenopausal women, we found that leisure physical activity was significantly related to a favorable lipid and lipoprotein subclass profile (i.e., higher levels of HDL-C and large HDL-P, and lower levels of triglycerides, and total and medium VLDL-P), regardless of HT use. However, we saw no association between leisure physical activity and LDL-C, which agrees with previous reports. The beneficial association that was observed in our study between leisure physical activity and higher large HDL-C and lower total and medium VLDL-P levels are congruent with the higher HDL-C and lower triglyceride levels, since those are the primary lipids carried by those particles, respectively. Generally, past investigations in postmenopausal women have shown that physical activity levels are beneficially related to both HDL-C and
triglyceride levels, and these associations remained after adjustment for factors such as body mass index and HT status (28, 29).

Findings from the current investigation also suggest that for several key lipoprotein subclass measures, the relationship with physical activity differed by HT use. After stratification by HT use, physical activity was independently related to larger mean HDL and LDL particle size, and lower levels of total and small LDL-P among non-HT users, but not among women currently taking HT. As we and others have shown, these particular lipoprotein subclass measures, particularly total LDL-P, are independently associated with coronary calcification (16) and predict incident CVD (14, 15) among postmenopausal women. Furthermore, in a study of healthy postmenopausal women, we have previously shown that higher levels of total and small LDL-P and small mean LDL particle size are associated with coronary artery calcification, for both HT users and non-users (17). Therefore, the results of the current study, showing that among HT users, higher levels of leisure physical activity was not associated with any improvements in these specific lipoprotein subclasses are particularly important. In HT users, the pharmacological effects of the hormones appears to have masked or interfered with the potential benefits of leisure physical activity levels on important facets of the lipoprotein subclass profile.

Past research exploring the relationship between physical activity and lipids in postmenopausal women has generated contradictory results (21). As previously mentioned, it has been suggested that estrogen may mask the response of lipid levels to participation in physical activity in postmenopausal women taking HT (30). Therefore, one possible reason for the divergent results of previous studies investigating the relationship between physical activity and lipid levels among postmenopausal women may be explained by the inconsistent selection of
the study population with regard to HT use. Results of the present investigation illustrate that the independent relationship between physical activity and certain lipoprotein subclasses, such as mean HDL and LDL particle size, total, and small LDL-P, may only become evident after stratification by HT status. It is, therefore, imperative for future work to consider HT use when examining the relationship between physical activity and lipids in postmenopausal women.

The present analysis utilized a questionnaire that assessed structured physical activity levels and demonstrated that leisure physical activity was related to many lipid and lipoprotein subclasses. Although questionnaires have been shown to accurately assess higher intensity, structured physical activities, they typically do a poor job when measuring lower intensity, unstructured lifestyle physical activities, such as household chores, childcare, and housework (22, 31). Future work should examine whether total physical activity levels, including both structured and unstructured activities as measured by an objective assessment tool, follows the same trends as what was observed in the present investigation. Also, the addition of an objective physical activity measure would allow investigators the opportunity to validate activity estimates obtained through subjective measures.

When interpreting the findings of the present investigation, a number of limitations need to be considered. Data from only one point in time, the baseline visit, was used in the analyses. Although informative, this cross-sectional study analysis is limited in that it does not provide information pertaining to the direction of association or allow us to determine how the relationship between physical activity and lipoprotein subclasses changes as a woman changes her physical activity levels, HT status, or both. In addition, the results were adjusted for lifestyle factors (age, BMI, dietary saturated fat and cholesterol intake) that have been demonstrated to be related to both physical activity and lipid and lipoprotein subclass levels. The adjustment of
results by these lifestyle factors helps to ensure that any significant relationship that was noted between physical activity and lipid and lipoprotein subclass levels is not the result of confounding by a third factor. Also, the results are limited by our small sample size which may reduce confidence in our findings. Specifically, post-hoc power analyses revealed that the power to examine the interaction between physical activity levels and hormone therapy status ranged from 61-75%. However, despite having relatively low power, the results were strong enough to detect a statistical significant difference. Finally, women were classified as current HT users or non-users; the type, dosage, and/or duration of HT usage were not considered in these analyses. Therefore, future work is needed to further investigate the complex relationship between HT, and mean lipoprotein subclass and physical activity levels.

In conclusion, the literature has been inconsistent with regards to the relationship between physical activity and lipids and lipoproteins in postmenopausal women. Findings from the present work confirmed earlier studies suggesting that, regardless of HT use, physical activity levels were directly related to HDL-C levels and indirectly related to triglyceride levels. However, when the results were stratified by HT use, physical activity was associated with key lipoprotein subclasses in HT non-users which have been shown to be related to both incident and subclinical CVD. These findings raise the important question as to whether the beneficial effect of physical activity on the lipid profile in postmenopausal women is similar between HT users and non-users.

As HT is being prescribed less frequently and for shorter periods of time, we need to be aware of other strategies to favorably alter the overall lipid profile in postmenopausal women. Despite the fact that these data are cross-sectional in nature, findings from the current
investigation suggest that the promotion of physical activity may be a safe and effective alternative to improve lipids and reduce risk of CVD in postmenopausal women.

Acknowledgements: The authors would like to acknowledge the contributions of the staff of the WOMAN study. This research was funded by National Heart, Lung, and Blood Institute contract R01-HL-66468.
4.6 REFERENCES


Table 4-1: Participant Characteristics Stratifying by Current Hormone Therapy Use in the WOMAN Study

<table>
<thead>
<tr>
<th></th>
<th>Entire Cohort</th>
<th>Hormone Therapy Users</th>
<th>Non-Hormone Therapy Users</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>56.9 (2.9)</td>
<td>56.6 (2.9)</td>
<td>57.3 (2.9)</td>
<td>0.0079</td>
</tr>
<tr>
<td><strong>Leisure Physical Activity (MET hr-wk)</strong></td>
<td>11.1 (5.3, 20.2)</td>
<td>12.8 (6.2, 21.5)</td>
<td>9.1 (4.3, 18.6)</td>
<td>0.0128</td>
</tr>
<tr>
<td><strong>Body Mass Index (kg/m2)</strong></td>
<td>30.7 (3.8)</td>
<td>30.7 (3.6)</td>
<td>30.8 (4.1)</td>
<td>0.8054</td>
</tr>
<tr>
<td><strong>Waist Circumference (cm)</strong></td>
<td>105.7 (11.2)</td>
<td>105.8 (10.6)</td>
<td>105.5 (12.0)</td>
<td>0.7489</td>
</tr>
<tr>
<td><strong>% High School Graduate</strong></td>
<td>98.7</td>
<td>99.0</td>
<td>98.5</td>
<td>0.6426</td>
</tr>
<tr>
<td><strong>% African American</strong></td>
<td>11.6</td>
<td>6.6</td>
<td>18.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>% Married</strong></td>
<td>66.8</td>
<td>69.6</td>
<td>62.8</td>
<td>0.1180</td>
</tr>
<tr>
<td><strong>% Current Smokers</strong></td>
<td>6.2</td>
<td>4.9</td>
<td>8.2</td>
<td>0.1474</td>
</tr>
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</table>

**Lipids**

<table>
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<tr>
<th></th>
<th>Entire Cohort</th>
<th>Hormone Therapy Users</th>
<th>Non-Hormone Therapy Users</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Cholesterol, mg/dL</strong></td>
<td>216.4 (28.1)</td>
<td>211.9 (26.6)</td>
<td>223.0 (29.1)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>LDL Cholesterol, mg/dL</strong></td>
<td>128.2 (25.0)</td>
<td>122.1 (22.8)</td>
<td>137.0 (25.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>HDL Cholesterol, mg/dL</strong></td>
<td>59.8 (13.9)</td>
<td>60.7 (13.8)</td>
<td>58.8 (14.0)</td>
<td>0.0828</td>
</tr>
<tr>
<td><strong>Triglyceride, mg/dL</strong></td>
<td>142.2 (74.7)</td>
<td>146.1 (81.0)</td>
<td>136.6 (64.2)</td>
<td>0.1733</td>
</tr>
</tbody>
</table>

**NMR Lipoprotein Particle Measures**

<table>
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<tr>
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<th>Entire Cohort</th>
<th>Hormone Therapy Users</th>
<th>Non-Hormone Therapy Users</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total LDL-P, nmol/L</strong></td>
<td>1394.1 (310.4)</td>
<td>1390.1 (296.2)</td>
<td>1400.0 (330.6)</td>
<td>0.7370</td>
</tr>
<tr>
<td><strong>LDL, nmol/L</strong></td>
<td>42.8 (36.3)</td>
<td>41.5 (35.7)</td>
<td>44.7 (37.2)</td>
<td>0.3423</td>
</tr>
<tr>
<td><strong>Large LDL-P, nmol/L</strong></td>
<td>640.5 (219.9)</td>
<td>632.3 (213.2)</td>
<td>652.5 (229.3)</td>
<td>0.3277</td>
</tr>
<tr>
<td><strong>Small LDL-P, nmol/L</strong></td>
<td>710.8 (419.3)</td>
<td>716.3 (399.4)</td>
<td>702.8 (447.8)</td>
<td>0.7326</td>
</tr>
<tr>
<td><strong>LDL Size, nm</strong></td>
<td>21.4 (0.7)</td>
<td>21.4 (0.7)</td>
<td>21.4 (0.7)</td>
<td>0.7348</td>
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<tr>
<td><strong>Total HDL-P, μmol/L</strong></td>
<td>35.0 (5.4)</td>
<td>35.4 (5.5)</td>
<td>34.6 (5.2)</td>
<td>0.1022</td>
</tr>
<tr>
<td><strong>Large HDL-P, μmol/L</strong></td>
<td>7.6 (3.2)</td>
<td>7.7 (3.3)</td>
<td>7.4 (3.1)</td>
<td>0.2878</td>
</tr>
<tr>
<td><strong>Medium HDL-P, μmol/L</strong></td>
<td>2.8 (3.3)</td>
<td>3.5 (3.6)</td>
<td>1.8 (2.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Small HDL-P, μmol/L</strong></td>
<td>24.6 (5.3)</td>
<td>24.1 (5.4)</td>
<td>25.3 (5.2)</td>
<td>0.0130</td>
</tr>
<tr>
<td><strong>HDL Size, nm</strong></td>
<td>9.1 (0.5)</td>
<td>9.1 (0.4)</td>
<td>9.0 (0.5)</td>
<td>0.0100</td>
</tr>
<tr>
<td><strong>Total VLDL-P, nmol/L</strong></td>
<td>83.3 (37.3)</td>
<td>80.8 (37.5)</td>
<td>87.0 (36.9)</td>
<td>0.0743</td>
</tr>
<tr>
<td><strong>Large VLDL-P, nmol/L</strong></td>
<td>4.9 (5.9)</td>
<td>5.3 (6.5)</td>
<td>4.3 (4.8)</td>
<td>0.0499</td>
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<tr>
<td><strong>Medium VLDL-P, nmol/L</strong></td>
<td>31.7 (24.7)</td>
<td>30.9 (24.9)</td>
<td>32.8 (24.4)</td>
<td>0.3970</td>
</tr>
<tr>
<td><strong>Small VLDL-P, nmol/L</strong></td>
<td>46.7 (17.9)</td>
<td>44.5 (17.5)</td>
<td>49.8 (18.2)</td>
<td>0.0016</td>
</tr>
</tbody>
</table>

Age, BMI, Waist Circumference, and Lipoprotein Subclasses represented as mean (standard deviation). Leisure Physical Activity represented as median (25th, 75th percentile). p value = hormone therapy users vs. non-hormone therapy users.
Table 4-2: Final Multivariate Linear Regression Model for Leisure Physical Activity and Lipoprotein Subclasses for the Entire Cohort (n=482)

<table>
<thead>
<tr>
<th></th>
<th>HDL-C (mg/dL)</th>
<th>Large HDL-P (µmol/L)</th>
<th>Total VLDL-P (nmol/L)</th>
<th>Medium VLDL-P (nmol/L)</th>
<th>Triglycerides (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leisure PA (MET hr-wk)</td>
<td>1.05 ± 0.39**</td>
<td>0.24 ± 0.08**</td>
<td>-3.11 ± 1.05**</td>
<td>-1.96 ± 0.70**</td>
<td>-5.78 ± 2.08**</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.26 ± 0.21</td>
<td>-0.04 ± 0.05</td>
<td>0.04 ± 0.58</td>
<td>-0.11 ± 0.38</td>
<td>-0.22 ± 1.15</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>-0.54 ± 0.17**</td>
<td>-0.14 ± 0.04**</td>
<td>0.75 ± 0.46</td>
<td>0.23 ± 0.30</td>
<td>2.45 ± 0.91**</td>
</tr>
<tr>
<td>Cholesterol/Saturated Fat Intake Index</td>
<td>-0.09 ± 0.05</td>
<td>-0.00 ± 0.01</td>
<td>0.05 ± 0.14</td>
<td>0.07 ± 0.09</td>
<td>0.13 ± 0.28</td>
</tr>
<tr>
<td>Hormone Therapy Status</td>
<td>-1.72 ± 1.28**</td>
<td>-0.19 ± 0.30</td>
<td>4.97 ± 3.46</td>
<td>1.34 ± 2.31</td>
<td>-7.07 ± 6.90</td>
</tr>
<tr>
<td>R²</td>
<td>0.049919</td>
<td>0.052433</td>
<td>0.33568</td>
<td>0.020394</td>
<td>0.036905</td>
</tr>
</tbody>
</table>

Final model adjusted for age, body mass index, cholesterol/saturated fat intake, and hormone therapy. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.
Table 4-3: Multivariate Linear Regression Model for Leisure Physical Activity and Lipoprotein Subclasses for Hormone Therapy Users and Non-Hormone Therapy Users

<table>
<thead>
<tr>
<th></th>
<th>Mean HDL Particle Size (nm)</th>
<th>Mean LDL Particle Size (nm)</th>
<th>Total LDL-P (nmol/L)</th>
<th>Small LDL-P (nmol/L)</th>
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<tr>
<td><strong>Model II Stratified by Hormone Therapy</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Non-Hormone Therapy Users (n=196)</strong></td>
<td></td>
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</tr>
<tr>
<td>Leisure PA (MET hr-wk)</td>
<td>0.05 ± 0.02**</td>
<td>0.06 ± 0.03*</td>
<td>-35.15 ± 14.47*</td>
<td>-46.41 ± 19.45*</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.01 ± 0.01</td>
<td>-0.00 ± 0.02</td>
<td>0.72 ± 7.90</td>
<td>2.77 ± 10.62</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>-0.02 ± 0.01**</td>
<td>-0.02 ± 0.01</td>
<td>10.78 ± 5.85</td>
<td>13.98 ± 7.86</td>
</tr>
<tr>
<td>Cholesterol/Saturated Fat Intake Index</td>
<td>0.00 ± 0.00</td>
<td>0.01 ± 0.00</td>
<td>-1.02 ± 1.98</td>
<td>-3.54 ± 2.66</td>
</tr>
<tr>
<td>R²</td>
<td>0.097946</td>
<td>0.076803</td>
<td>0.065444</td>
<td>0.079416</td>
</tr>
<tr>
<td><strong>Hormone Therapy Users (n=286)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leisure PA (MET hr-wk)</td>
<td>-0.01 ± 0.02</td>
<td>-0.02 ± 0.03</td>
<td>8.38 ± 10.85</td>
<td>8.33 ± 14.64</td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.01 ± 0.01</td>
<td>0.01 ± 0.01</td>
<td>-0.95 ± 6.03</td>
<td>-4.54 ± 8.13</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>-0.03 ±</td>
<td>-0.03 ± 0.01*</td>
<td>11.54 ± 5.01*</td>
<td>14.39 ± 6.76*</td>
</tr>
<tr>
<td></td>
<td>0.01***</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol/Saturated Fat Intake Index</td>
<td>-0.00 ± 0.00</td>
<td>0.00 ± 0.00</td>
<td>-0.16 ± 1.44</td>
<td>-0.63 ± 1.95</td>
</tr>
<tr>
<td>R²</td>
<td>0.053346</td>
<td>0.022870</td>
<td>0.020586</td>
<td>0.019779</td>
</tr>
</tbody>
</table>

Multivariate models adjusted for age, BMI, and cholesterol/saturated fat intake. *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.
Figure 4-1: Mean Lipoprotein Subclass Levels by Leisure Physical Activity, stratified by Current Hormone Therapy Use. Quartile 1: <5.3 MET hr-wk; Quartile 2: >5.3 to <11.3 MET hr-wk; Quartile 3: >11.3-20.4 MET hr-wk; Quartile 4: >20.4 MET hr-wk
CAN A LIFESTYLE INTERVENTION ATTENUATE THE EFFECT OF DISCONTINUING HORMONE THERAPY ON CARDIOVASCULAR RISK FACTORS?

For Future Publication

Kelley K. Pettee PhD\textsuperscript{1}, Andrea M. Kriska PhD\textsuperscript{1}, Molly B. Conroy\textsuperscript{1,2} MD, B. Delia Johnson PhD\textsuperscript{1}, Trevor J. Orchard\textsuperscript{1} MD, Bret H. Goodpaster\textsuperscript{2} PhD, Frani M. Averbach\textsuperscript{1} MPH, Lewis H. Kuller\textsuperscript{1} MD

\textsuperscript{1}Department of Epidemiology

\textsuperscript{2}Division of General Internal Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA
5.1 ABSTRACT

**OBJECTIVE:** To determine if a lifestyle intervention consisting of physical activity and dietary modifications can counteract unfavorable CVD risk factor changes that are predicted to occur as postmenopausal women discontinue hormone therapy (HT) use. **DESIGN:** Participants from the Woman On the Move through Activity and Nutrition (WOMAN) study were randomized at baseline to either a health education (HE) or lifestyle change (LC) group. The impact of a lifestyle intervention on CVD risk factor reduction was examined in the 231 postmenopausal [mean age 58.3 (2.9 years)] women who were initially on HT at baseline and either remained on HT (n=106) or discontinued use (n=125) by the 18 month follow up visit. **RESULTS:** In general, lifestyle intervention had a beneficial impact on CVD risk factor reduction regardless of HT status at 18 months. Women randomized to the LC group decreased weight, BMI, WC, insulin and triglyceride levels and improved glucose levels when compared to the HE group. Within the HE arm, women who discontinued HT had significantly (p<0.01) higher increases in total and LDL-C as compared to HT continuers, whereas no such differences were observed in the LC arm. **CONCLUSIONS:** A lifestyle based intervention comprised of physical activity and diet was effective for CVD risk factor reduction among postmenopausal women. Negative lipid consequences of discontinuing HT were noted only in the HE group and not among women randomized to the LC group. These findings suggest that a lifestyle behavioral approach can successfully attenuate increases in total and LDL-C that result from HT discontinuation.
5.2 INTRODUCTION

After menopause, women experience an increased incidence of cardiovascular disease (CVD) (1). The increase in CVD incidence is likely due to detrimental changes in related risk factors, such as dyslipidemia, abdominal adiposity, hypertension, and insulin resistance that often worsen during the menopausal transition (2, 3). Hormone therapy (HT) use has been shown to favorably alter CVD risk factors (4) and, until recently, was widely prescribed for both the relief of menopausal symptoms and general CVD prevention in postmenopausal women (5, 6).

Past observational studies have consistently suggested an inverse association between exogenous HT use and CVD (7, 8), due in part to the beneficial impact of HT on CVD risk factors. The Postmenopausal Estrogen/Progestin Interventions (PEPI) study was a randomized clinical trial exploring the impact of four HT regimens (placebo control vs. unopposed estrogen or one of three estrogen/progestin combinations) on selected CVD risk factors in healthy postmenopausal women (9). Results from the PEPI trial suggest that, regardless of type of HT, HT users had increased HDL cholesterol (HDL-C) and decreased LDL cholesterol (LDL-C) and fasting glucose levels when compared to the placebo control group (9).

In contrast to observational studies, evidence from recent clinical trials, such as the Women’s Health Initiative (WHI) (10, 11) and Heart and Estrogen/progestin Replacement Study (HERS) (12) have failed to confirm the cardio-protective benefits of hormone therapy (HT) (7, 8). Following the publication of the WHI results, many HT users were advised by their physicians to taper doses and/or discontinue use (5). Unfortunately, there is little information regarding the health impact of the widespread discontinuation of HT.
The Women On the Move through Activity and Nutrition (WOMAN) study is a five year randomized clinical trial of primary CVD prevention among postmenopausal women designed to test whether an aggressive non-pharmacological lifestyle intervention will modify or reduce measures of subclinical CVD. Approximately midway through the WOMAN study recruitment process, results were publicized from the estrogen/progestin (E+P) arm of the WHI trial indicating adverse effects among HT users (11). Women who had already been randomized into the WOMAN study were advised by their health care provider to taper and/or discontinue HT use according to the new guidelines based upon the WHI results. The WOMAN study provides a unique opportunity to explore the impact of HT discontinuation and the possible attenuation of this impact by healthy lifestyle behaviors on CVD risk factors after 18 months of a behavioral lifestyle intervention.

Based on results from previous studies (9), it is hypothesized that HT discontinuation will negatively impact certain CVD risk factors such as lipids. The purpose of this current longitudinal investigation is to determine if a lifestyle intervention consisting of healthy physical activity and dietary practices can lessen unfavorable CVD risk factor changes that are hypothesized to occur as women discontinue HT use after 18 months of study participation.

5.3 METHODS

5.3.1 Study Population

Five hundred and eight postmenopausal women were recruited for the WOMAN study, primarily through direct mailing from selected zip codes in Allegheny County, Pennsylvania from April
2002 to October 2003. Eligibility criteria for enrollment into the study included waist circumference (WC) \( \geq 80 \) centimeters (cm), body mass index (BMI) between 25 – 39.9 kilograms per meters squared (kg/m\(^2\)), not currently taking lipid lowering drugs and having a low density lipoprotein (LDL-c) level between 100 - 160 milligrams per deciliter (mg/dL), no physical limitations that would preclude walking, no known diabetes, and no diagnosed psychotic disorder or depression. All participants provided written informed consent and all protocols were approved by the institutional review board at the University of Pittsburgh. Results from the current investigation were generated from data collected at baseline and at the 18 month clinic visit.

5.3.2 Group Randomization: Intervention Design

Eligible women were randomized to a Health Education (HE) comparison group or a Lifestyle Change (LC) group using a block randomized design prepared by a statistician. Briefly, women in the HE group received educational lectures while women randomized to the LC group received group and individualized intervention which focused on body weight and WC reduction through healthy lifestyle changes. The healthy lifestyle behaviors promoted in the LC included 150 minutes per week of moderate intensity physical activity similar to brisk walking and a caloric intake of 1300-1500 calories per day, emphasizing an eating pattern low in total (<17%) and saturated fat (<7%).
5.3.3 Physical Activity

Physical activity was measured using the past year version of the Modifiable Activity Questionnaire (MAQ), an interviewer administered questionnaire (13). This questionnaire assesses leisure and occupational activities, as well as extreme levels of inactivity due to disability. For the purposes of this investigation, we will focus on the leisure physical activity estimate as there was little reported occupational physical activity in our study population. Study participants were asked to identify if they participated in a variety of specific activities, such as walking for exercise, at least 10 times over the past year (12 months). For each activity identified, they were asked which months they had participated in that specific activity over the past year and then estimated the number of times each month and length of time that they spent doing the specific activity. Physical activity levels were calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the metabolic equivalent (MET) of that activity and summed for all activities performed. One MET represents the energy expenditure for an individual at rest, whereas a 10-MET activity requires 10 times the resting energy expenditure (14). Leisure physical activity data were expressed as metabolic equivalent hours per week (MET hr-wk). The MAQ has been shown to be both reliable (13, 15) and valid (13, 15, 16). In the WOMAN study, baseline and 18 month physical activity estimates obtained from the MAQ were positively and significantly (p<0.0001) correlated with step counts obtained from a pedometer step counter (rho = 0.30 and 0.36, respectively).
5.3.4 Hormone Therapy Groups

Information on HT use was obtained through self-report in addition to a medication inventory that was completed at both the baseline and 18 month clinic visit. Following the publication of the WHI results, study participants were allowed to enter the trial after recently terminating HT use; however, only those who were identified as current HT users at baseline were included in the current report. These women were classified into one of two HT groups: 1). HT Continuers (HT user at baseline and 18 months) and 2). HT Discontinuers (HT user at baseline and non-user at 18 months).

5.3.5 Clinical Measures

All clinical measures were obtained at the baseline and 18 month follow-up clinic visit. Clinical measures included height, body weight, waist circumference, and a fasting (12 hour) blood draw. BMI was calculated from height and weight measured with a stadiometer and calibrated balance beam scale by dividing the participant’s weight in kilograms by the square of her height in meters. Waist circumference (WC) was measured at the navel (horizontal plane at the center of the navel) using a fiberglass retractable tape measure. Total cholesterol, HDL-C, triglycerides, and glucose were determined by conventional methods. LDL-C was estimated by the Friedewald equation and insulin was measured via radioimmunoassay.
5.3.6 Other Measures

In addition to the clinical measures, a saturated fat/cholesterol intake index score was calculated using the Connor Diet Habit Survey, which has been shown to be both a reliable and valid measure for the rapid assessment of eating habits and diet composition. The saturated fat and cholesterol score is generated by summing the scores for 20 questions related to cholesterol and saturated fat intake (17).

5.3.7 Statistical Methods

Descriptive statistics were used to describe baseline anthropometric measures, leisure physical activity levels, and CVD risk factor levels by HT use at the 18 month follow-up visit. Normally distributed variables were reported as mean ± standard deviation; non-normally distributed variables were reported as median with 25th and 75th percentiles. Depending upon the characteristics of the variable, t-tests or Wilcoxon Rank Sum tests were used to compare baseline CVD risk factor values between HT continuers and HT discontinuers.

The 18 month change in anthropometric, physical activity, and CVD risk factor levels variables over time was calculated as the difference in values between the 18 month follow-up and baseline. Change variables were compared between HT continuers and HT discontinuers, stratified by treatment group assignment using t-tests or Wilcoxon Rank Sum tests. CVD risk factor change was also reported and compared between randomized groups, stratified by HT status at the 18 month clinic visit.

Further post-hoc analyses were conducted to determine the independent effect of healthy lifestyle behaviors that were promoted in the lifestyle intervention on CVD risk factor reduction.
using multivariate linear regression models. The multivariate model examined the longitudinal relationship between CVD risk factor and change in leisure physical activity, and saturated fat/cholesterol intake, after adjusting for HT status at 18 months and baseline levels of leisure physical activity, saturated fat/cholesterol intake, and relevant CVD risk factor.

5.4 RESULTS

Of the 508 women randomized into the WOMAN study, 455 (90%) completed the 18 month clinic visit. Of these 455 women, 182 reported not using HT at baseline and were excluded from these analyses. Also excluded were 16 women initiating a lipid lowering medication during the 18 month interval and 26 with incomplete physical activity, clinical, or diet quality data. Women not using HT at baseline were more likely to be African American, had lower reported leisure physical activity levels, and higher baseline total cholesterol, LDL-C, insulin, and glucose levels when compared to women who were HT users at baseline (p<0.05).

The 231 women included in the present analyses had a mean age of 58.3 (2.9 years). The mean BMI was 28.5 (4.3) kg/m² and average WC was 98.4 (11.9) cm. Additionally, 98.7% had at least a high school degree, 6.9% were African American, and 4.8% were current smokers. One hundred and six (106; 46%) of the 231 women were HT continuers and the remaining 125 (54%) women were HT discontinuers at 18 months. Of the HT discontinuers, 61% had HT discontinued prior to the 6 month follow-up visit. There were no significant differences between HT continuers and HT discontinuers with regards to education, race, or smoking status (data not shown).
Table 5.1 describes and compares CVD risk factor levels between HT continuers vs. HT discontinuers at baseline. Women in the HT continuer group were significantly (p<0.05) younger than women who discontinued HT. However, the two HT groups did not significantly differ in anthropometric and clinical measures, leisure physical activity, saturated fat/cholesterol intake, lipid, or glucose levels. One notable exception was that women who continued HT at 18 months had lower baseline insulin levels when compared to HT discontinuers.

The lifestyle intervention was successful and had a positive impact on many CVD risk factors among both HT continuers and HT discontinuers (Table 5.2). More specifically, when compared to the HE group, the LC group significantly decreased weight, BMI, average WC, and saturated fat and cholesterol intake and increased leisure physical activity levels (significant in HT discontinuers only). With regards to CVD risk factor change, women in the LC group had improved insulin (significant in HT continuers only), triglyceride and glucose levels (significant in HT discontinuers only) when compared to the HE group. There were no significant differences at 18 months between randomized groups with regards to changes in HDL-C, systolic and diastolic blood pressure levels in either HT continuers or HT discontinuers.

In contrast, there was marked differences by randomized group assignment between HT continuers and HT discontinuers with regards to two key CVD risk factors; total cholesterol and LDL-C (Figure 5.1). When comparing total cholesterol and LDL-C change within the HE arm, women who had discontinued HT use had significantly higher increases in these two measures as compared to HT continuers [total cholesterol: 21.4 vs. 3.5 mg/dL (p = 0.0063) and LDL-C: 21.7 vs. 4.0 mg/dL (p = 0.0017)]. The significant differences in total and LDL cholesterol change between HT continuers and HT discontinuers were not replicated in the LC arm [total cholesterol: 5.8 vs. 4.7 mg/dL (p = 0.8225) and LDL-C: 6.1 vs. 7.4 mg/dL (p = 0.7572)].
were no other differences between HT groups with regards to CVD risk factor change in either the HE or LC group.

Since it appeared that lifestyle intervention had a major impact on CVD risk factors in postmenopausal women, post-hoc analysis was performed to begin to examine the role of the specific components of the lifestyle intervention on risk factor reduction. Specifically, the effect of leisure physical activity and diet on CVD risk factor reduction was examined in the entire cohort (Table 5.3). After adjustment for HT use at the 18 month clinic visit, baseline leisure physical activity, saturated fat and cholesterol intake, and relevant CVD risk factor level (i.e. adjustment for baseline HDL-C when exploring HDL-C change), an increase in leisure physical activity was significantly related (p<0.05) to decreases in triglyceride levels and increases in HDL-C levels as well as decreases in LDL-C and glucose levels (p<0.10). With regards to dietary behavior, an improvement in saturated fat and cholesterol intake was significantly related to decreases in total cholesterol, LDL-C, triglyceride, insulin, and glucose levels (p<0.05).

5.5 DISCUSSION

The present investigation explored the effect of lifestyle intervention on CVD risk factors in postmenopausal women that were on HT at baseline and either continued or discontinued use after 18 months of study participation. Prior to the WOMAN study, the beneficial effect of a lifestyle intervention for CVD risk factor reduction had not been examined in women who had recently discontinued HT. When considering the current controversies regarding HT use, the findings from the present report are timely.
Regardless of HT status at 18 months, women randomized to the LC group increased leisure physical activity levels, improved saturated fat and cholesterol intake and glucose levels, and decreased weight, BMI, WC, insulin and triglyceride levels when compared to the HE group. The overall success of the WOMAN study lifestyle intervention was in line with the findings from previous reports suggesting the efficacy of lifestyle based approaches for risk factor reduction and chronic disease prevention in populations at risk for diabetes (18-21) and heart disease (22). Specifically in older women, lifestyle intervention was demonstrated to prevent weight gain (23) and to determine a rise in LDL-C levels (24) during the menopausal transition.

However, previous reports did not account for concurrent changes in HT status, an issue which has become particularly relevant in the post-WHI era. The WOMAN study provided the unique opportunity to examine the effect of a lifestyle intervention on CVD risk factor reduction by change in HT status. Based on findings from previous investigations, it was assumed that HT discontinuation would result in unfavorable changes to CVD risk factors (9). As predicted, the WOMAN study documented that HT discontinuation at 18 months resulted in increases in total cholesterol and LDL-C levels in the HE group. In contrast, in the LC group, there were no observed differences between HT groups with regards to these particular lipids. These findings suggest that a lifestyle intervention, consisting of physical activity, dietary behavior modification, and weight loss can successfully attenuate unfavorable changes to CVD risk factors that result from HT discontinuation. These results have important public health implications and suggest that a non-pharmacological approach is both a safe and effective strategy for CVD risk factor reduction in postmenopausal women, especially for women that discontinued HT use.
The WOMAN study was not designed to determine the independent contribution of the specific intervention components on CVD risk factors. However, post-hoc analyses were conducted to begin to examine the role of the specific components of the lifestyle intervention for CVD risk factor reduction. Increases in leisure physical activity were independently related to increases in HDL-C and decreases in triglyceride levels. Likewise, improved saturated fat and cholesterol intake was independently related to decreases in total cholesterol, LDL-C, triglyceride, insulin, and glucose levels. The independent contribution of physical activity and diet on these particular lipid measures was similar in both HT continuers and discontinuers.

CVD continues to be the leading cause of morbidity and mortality among women in westernized countries (1). However, CVD in women has been underappreciated by the public (25) and under treated by health care providers (24, 27). Recent public health campaigns, such as the American Heart Association’s “Go Red for Women” campaign (28) have raised public health awareness of the disease. However, concern and confusion about the risks associated with HT has left women and their health care providers searching for safe and effective means to reduce CVD risk factors.

In this era of uncertainty, one potential consequence of diminished HT use for CVD risk factor reduction is increased use of supplementary pharmacological agents, such as statins and aspirin; however, both are associated with side effects (29, 30). In addition, trial data suggests that aspirin does not protect women from CVD in a similar fashion to men (31). Furthermore, the majority of statin research to date has been conducted in men (32, 33). However, based on the promising findings of the current investigation, special attention should be paid to encouraging efficacious lifestyle strategies that are likely to impart more benefit and less risk than drug therapies.
When interpreting the findings from the present investigation, a number of limitations need to be considered. The present analyses utilized self-reported estimates of leisure physical activity levels and dietary intake which may be subject to recall bias. Also, since this was a behavioral intervention, there may have been a differential reporting bias with the intervention group reporting what they should be doing rather than what they are doing. However, it should be noted that the leisure physical activity estimates obtained via the MAQ were validated with pedometer step counts in the WOMAN study population. In addition, WOMAN study participants were not randomized to continue or discontinue HT use at 18 months, which may influence the findings of the current report. In addition, the duration of prior HT usage and/or time since discontinuation were not considered in these analyses. Finally, for the purposes of this report, saturated fat and cholesterol intake was used as general measure of diet composition. Therefore, future work is needed to investigate the overall contribution of diet on CVD risk factor reduction.

In conclusion, little data has been available regarding the widespread impact of the WHI results on CVD risk factor change in postmenopausal women. The current report confirmed previous findings suggesting that a lifestyle based approach is effective for general CVD risk factor reduction. In addition, lifestyle interventions incorporating physical activity and dietary modification can successfully attenuate negative changes to lipids that result from HT discontinuation. More research and improved delivery systems are needed to facilitate dissemination and maintenance of healthy lifestyle programs in postmenopausal women.
Acknowledgements: The authors would like to acknowledge the 508 dedicated WOMAN study participants and the contributions of the WOMAN study staff, including Alhaji Buhari, Eileen Cole, Phyllis Jones, Laura Kinzel, Barbara Kolodziej, Wm. Scott Pappert, and Darcy Underwood. This research was funded by National Heart, Lung, and Blood Institute contract R01-HL-6646.
5.6 REFERENCES


<table>
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<tr>
<th></th>
<th>HT Continuers (n=106)</th>
<th>HT Discontinuers (n=125)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.9 (2.8)</td>
<td>58.7 (2.9)</td>
<td>0.04</td>
</tr>
<tr>
<td>Weight, lbs.</td>
<td>178.2 (24.7)</td>
<td>180.4 (25.3)</td>
<td>0.51</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>30.4 (3.5)</td>
<td>30.8 (3.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>Waist Circumference, cm</td>
<td>105.5 (10.1)</td>
<td>107.1 (11.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Leisure Physical Activity, MET hr-wk</td>
<td>13.6 (6.7, 20.6)</td>
<td>10.9 (4.9, 20.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Saturated Fat/Cholesterol Intake Index</td>
<td>62.1 (12.5)</td>
<td>60.8 (12.7)</td>
<td>0.42</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg</td>
<td>124.7 (13.6)</td>
<td>122.8 (13.3)</td>
<td>0.28</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td>76.4 (9.1)</td>
<td>76.0 (7.8)</td>
<td>0.71</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>212.8 (23.7)</td>
<td>207.2 (26.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>LDL Cholesterol, mg/dL</td>
<td>122.4 (21.1)</td>
<td>118.7 (20.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>HDL Cholesterol, mg/dL</td>
<td>62.0 (14.5)</td>
<td>60.8 (13.1)</td>
<td>0.52</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>141.9 (69.0)</td>
<td>137.4 (74.4)</td>
<td>0.64</td>
</tr>
<tr>
<td>Insulin, mg/dL</td>
<td>11.6 (4.6)</td>
<td>13.6 (7.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>92.3 (7.7)</td>
<td>94.3 (9.9)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Baseline leisure physical activity levels presented as median (25th, 75th percentile); the remaining variables as mean (SD).
Table 5-2: 18 Month Change in Cardiovascular Risk Factors by Hormone Therapy Group and Randomized Group Assignment (n=231)

<table>
<thead>
<tr>
<th></th>
<th>HT Continuers</th>
<th>HT Discontinuers</th>
<th>P value</th>
<th>HE (n=45)</th>
<th>LC (n=61)</th>
<th>P value</th>
<th>HE (n=57)</th>
<th>LC (n=68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, lbs.</td>
<td>-5.3 (13.2)</td>
<td>-17.0 (13.7)</td>
<td>&lt;0.0001</td>
<td>4.3 (11.8)</td>
<td>-18.3 (17.7)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>-0.9 (2.1)</td>
<td>-3.0 (2.4)</td>
<td>&lt;0.0001</td>
<td>-0.9 (2.1)</td>
<td>-3.2 (3.1)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist Circumference, cm</td>
<td>-5.3 (6.4)</td>
<td>-10.6 (7.6)</td>
<td>0.0002</td>
<td>-3.8 (6.4)</td>
<td>-11.0 (8.5)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leisure Physical Activity, MET hr-wk</td>
<td>0.4 (-6.4, 9.3)</td>
<td>3.7 (-2.2, 12.0)</td>
<td>0.1955</td>
<td>0.8 (-4.8, 6.0)</td>
<td>7.2 (1.2, 12.7)</td>
<td>0.0012</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturated Fat/Cholesterol Intake Index</td>
<td>8.3 (11.1)</td>
<td>18.4 (14.1)</td>
<td>&lt;0.0001</td>
<td>5.2 (8.6)</td>
<td>20.3 (16.6)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CVD Risk Factors**

<table>
<thead>
<tr>
<th></th>
<th>HT Continuers</th>
<th>HT Discontinuers</th>
<th>P value</th>
<th>HE (n=45)</th>
<th>LC (n=61)</th>
<th>P value</th>
<th>HE (n=57)</th>
<th>LC (n=68)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, mg/dL</td>
<td>1.2 (4.1)</td>
<td>-0.5 (4.0)</td>
<td>0.0402</td>
<td>1.1 (8.4)</td>
<td>-0.1 (5.1)</td>
<td>0.3461</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>-10.0 (43.8)</td>
<td>-11.0 (53.5)</td>
<td>0.9192</td>
<td>1.6 (50.9)</td>
<td>-16.9 (48.2)</td>
<td>0.0399</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>5.2 (7.6)</td>
<td>2.2 (9.6)</td>
<td>0.0778</td>
<td>8.5 (13.0)</td>
<td>3.9 (9.0)</td>
<td>0.0264</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL Cholesterol, mg/dL</td>
<td>1.5 (11.6)</td>
<td>1.9 (10.1)</td>
<td>0.8619</td>
<td>-0.3 (11.2)</td>
<td>-0.2 (10.9)</td>
<td>0.9389</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg</td>
<td>-1.8 (18.2)</td>
<td>-2.7 (14.3)</td>
<td>0.7842</td>
<td>-2.6 (11.9)</td>
<td>-3.6 (14.3)</td>
<td>0.6750</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td>-0.09 (9.8)</td>
<td>-0.1 (9.1)</td>
<td>0.9820</td>
<td>-1.0 (7.2)</td>
<td>-1.9 (7.9)</td>
<td>0.5217</td>
<td></td>
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</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>3.5 (31.5)</td>
<td>5.8 (25.8)</td>
<td>0.6871</td>
<td>21.4 (32.9)</td>
<td>4.7 (30.3)</td>
<td>0.0041</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL Cholesterol, mg/dL</td>
<td>4.0 (26.1)</td>
<td>6.1 (22.5)</td>
<td>0.6607</td>
<td>21.7 (29.4)</td>
<td>7.4 (25.0)</td>
<td>0.0045</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

18 month change in leisure physical activity levels presented as median (25th, 75th percentile); the remaining 18 month change variables as mean (SD).
### Table 5-3: 18 Month Change in Cardiovascular Risk Factors after Adjustment (MLR Models) (n=231)

<table>
<thead>
<tr>
<th></th>
<th>Total Cholesterol, mg/dL</th>
<th>LDL Cholesterol, mg/dL</th>
<th>HDL Cholesterol, mg/dL</th>
<th>Triglycerides, mg/dL</th>
<th>Insulin, mg/dL (n=208)</th>
<th>Glucose, mg/dL (n=230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormone Therapy Use at 18 Months</td>
<td>3.8 ± 3.5</td>
<td>5.8 ± 3.0†</td>
<td>-2.1 ± 1.3†</td>
<td>1.4 ± 6.0</td>
<td>1.1 ± 0.7</td>
<td>3.1 ± 1.2**</td>
</tr>
<tr>
<td>△ Leisure Physical Activity (LPA), MET hr-wk</td>
<td>-2.1 ± 2.0</td>
<td>-3.3 ± 1.7†</td>
<td>2.9 ± 0.7****</td>
<td>-9.0 ± 3.5**</td>
<td>-0.5 ± 0.4</td>
<td>-1.2 ± 0.7†</td>
</tr>
<tr>
<td>△ Saturated Fat/Cholesterol Intake Score</td>
<td>-0.7 ± 0.1****</td>
<td>-0.5 ± 0.1****</td>
<td>-0.04 ± 0.05</td>
<td>-0.7 ± 0.2***</td>
<td>-0.1 ± 0.02****</td>
<td>-0.1 ± 0.04**</td>
</tr>
<tr>
<td>Baseline LPA, MET hr-wk</td>
<td>-0.5 ± 1.1</td>
<td>-1.5 ± 1.0</td>
<td>1.6 ± 0.4****</td>
<td>-1.4 ± 1.9</td>
<td>-0.2 ± 0.2</td>
<td>-0.8 ± 0.4*</td>
</tr>
<tr>
<td>Baseline Saturated Fat/Cholesterol Intake Score</td>
<td>-0.1 ± 0.1</td>
<td>-0.08 ± 0.1****</td>
<td>-0.07 ± 0.05</td>
<td>0.1 ± 0.2</td>
<td>-0.07 ± 0.03**</td>
<td>-0.05 ± 0.05</td>
</tr>
<tr>
<td>Baseline CVD Risk Factor Level</td>
<td>-0.5 ± 0.07****</td>
<td>-0.6 ± 0.07****</td>
<td>-0.3 ± 0.05****</td>
<td>-0.2 ± 0.04****</td>
<td>-0.5 ± 0.06****</td>
<td>-0.5 ± 0.07****</td>
</tr>
<tr>
<td>R²</td>
<td>0.317</td>
<td>0.318</td>
<td>0.274</td>
<td>0.212</td>
<td>0.349</td>
<td>0.252</td>
</tr>
</tbody>
</table>

*All models were adjusted for HT use at 18 months, change (△) in leisure physical activity levels, △ in saturated fat/cholesterol intake score, baseline leisure physical activity levels, baseline saturated fat/cholesterol intake score, and baseline levels of relevant CVD risk factor. †<0.10; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001.
Figure 5-1: 18 Month Change in Total Cholesterol and LDL-C by Randomized Group Assignment and HT group (**p<0.01)
ASSOCIATIONS BETWEEN WALKING PERFORMANCE DETERMINED BY THE LONG DISTANCE CORRIDOR WALK, PHYSICAL ACTIVITY LEVELS, AND SUBCLINICAL MEASURES OF CARDIOVASCULAR DISEASE IN POSTMENOPAUSAL WOMEN

For Future Publication

Kelley K. Pettee PhD¹, Beth M. Larouere PhD², Andrea M. Kriska PhD¹, B. Delia Johnson PhD¹, Bret H. Goodpaster³ PhD, Trevor J. Orchard¹ MD, Rachel H. Mackey PhD¹, Molly B. Conroy¹,³ MD, Darcy A. Underwood BS¹, Lewis H. Kuller¹ MD

¹ Department of Epidemiology
² Department of Health, Physical and Recreational Education
³ Division of General Internal Medicine, Department of Medicine, University of Pittsburgh, Pittsburgh, PA
6.1 ABSTRACT

**OBJECTIVE:** To examine the association between the long distance corridor walk (LDCW), physical activity levels, and measures of subclinical cardiovascular disease (CVD) in order to determine the construct validity of the LDCW to estimate health and functional status in middle-aged, postmenopausal women. **DESIGN:** The cross-sectional relationships between walk time from the LDCW, physical activity levels, and subclinical CVD measures were examined prior to group randomization in 492 [mean age 57.0 (2.9 years)] Caucasian and African-American women from the Woman On the Move through Activity and Nutrition (WOMAN) study. The WOMAN study is a randomized clinical trial involving overweight, middle-aged, postmenopausal women. **RESULTS:** Longer walk times were significantly associated with higher BMI (p<0.0001) and WC (p<0.0001) and lower subjective and objective physical activity levels (p<0.003). The proportion of detectable coronary artery calcification (CAC) and median aortic pulse wave velocity (aPWV) levels, both subclinical measures of CVD, were significantly higher among those with slower walk times (p<0.002 and p<0.001, respectively). **CONCLUSIONS:** Total walk time from the LDCW was significantly associated with both physical activity levels and measures of subclinical CVD. These findings support the utility of the LDCW to monitor patient progress in physical activity programs and/or identify those individuals who may warrant additional CVD screening.
6.2 INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death among women in the United States, claiming approximately 500,000 lives each year (1). A large proportion of deaths attributable to CVD occur in women with no prior symptoms (2, 3). Therefore, the identification of high risk, asymptomatic women who may benefit from primary CVD prevention would have important public health implications.

Past epidemiological studies have suggested that exercise capacity and/or cardiovascular fitness is an independent predictor of cardiovascular events and death among asymptomatic women (3, 4), thereby providing a general indicator of cardiovascular health status (5). Maximal oxygen uptake (VO$_2$ max) is the most accurate assessment technique to evaluate cardiovascular fitness and is typically measured using treadmill based protocols (5). However, VO$_2$ max protocols may not be practical in large epidemiological studies due to time constraints, staff burden, high equipment costs, and safety concerns (6). In instances where VO$_2$ max tests are not feasible, tests of walking endurance have been substituted for this gold standard measure to estimate fitness levels and overall health status (7-9).

Walking endurance protocols, such as the 6-minute walk test and long distance corridor walk (LDCW) were developed, and have been primarily used, in diseased and/or in older populations as a crude measure of fitness and health and functional status. The 6-minute walk test has primarily been used to estimate health status in populations with debilitating conditions such as chronic obstructive lung disease, heart failure, and left ventricular dysfunction (10-12), but has also been used to estimate functional status in older adults (13). The LDCW is a modification of the 6-minute walk test and uses a predetermined distance (400 meters) rather than duration (9). Time based tests of walking endurance evolved into distance based protocols
based on the notion that an individual may be more intrinsically motivated to complete a predetermined distance in as little time as possible, thus, providing a more maximal effort (9).

In contrast to the 6 minute walk test which is primarily used in diseased populations, the LDCW has been utilized in well-functioning, healthy older individuals with promising results. Results from a cross-sectional investigation suggested that walking performance was influenced by both clinical and subclinical disease and was strongly related to anthropometric measures and self reported physical activity levels (14). The usefulness of the LDCW to provide a general indicator of overall health in older adults was confirmed in the follow-up, longitudinal investigation. Results from this report suggested that exclusion or inability to complete the LDCW protocol was associated with an increased risk of mortality, incident CVD, and mobility limitation (7). Furthermore, among those that completed the protocol, each additional minute of walk time was associated with a 29% higher rate of mortality, a 20% higher rate of incident CVD, and 52% higher rates of mobility limitation and disability (7). In addition, unlike the 6 minute walk test, the LDCW has been shown to be a valid estimate of peak VO$_2$ (8) in older adults. These findings suggest that measured parameters from the LDCW, particularly walk time, are useful for estimating fitness levels as well as risk of mortality and/or disease among older adults.

It is fairly well established in the literature that the LDCW can be used as a low cost alternative for estimating fitness levels, functional status, and future morbidity and/or mortality in older individuals; however, little is known regarding the applicability of this test in younger populations. Thus, the primary purpose of the current report was to determine the construct validity of walk time from the LDCW against subjective and objective physical activity
assessments and measures of subclinical CVD in order to determine the utility of the LDCW to estimate functional status in middle-aged, postmenopausal women.

6.3 METHODS

6.3.1 Study Population

Five hundred and eight postmenopausal women were recruited for the Women On the Move through Activity and Nutrition (WOMAN) study, primarily through direct mailing from selected zip codes in Allegheny County, Pennsylvania from April 2002 to October 2003. The (WOMAN) study is a five year primary CVD prevention randomized clinical trial, designed to test whether an aggressive non-pharmacological lifestyle intervention among postmenopausal women will reduce measures of subclinical CVD. Eligibility criteria for enrollment into the study included waist circumference $\geq 80$ centimeters (cm), body mass index (BMI) between 25 – 39.9 kilograms per meters squared (kg/m$^2$), not currently taking lipid lowering drugs and having a low density lipoprotein cholesterol (LDL-C) level between 100 - 160 milligrams per deciliter (mg/dL), no physical limitations that would preclude walking, no known diabetes, and no diagnosed psychotic disorder or depression. All participants provided written informed consent and all protocols were approved by the institutional review board at the University of Pittsburgh. Results were based on data collected prior to randomization at the baseline clinic visit (2002-2003).
6.3.2 Demographic and Clinical Measures

Demographic factors and clinical measures were obtained at the baseline clinic visit. Clinical measures included height, body weight, average waist circumference (WC), and a fasting (12 hour) blood draw. Body mass index (BMI) was calculated from height and weight measured with a stadiometer and calibrated balance beam scale by dividing the participant’s weight in kilograms by the square of her height in meters. Average WC was measured at the navel (horizontal plane at the center of the navel) using a fiberglass retractable tape measure. Total cholesterol, HDL-C, triglycerides, and glucose were determined by conventional methods. LDL-C was estimated by the Friedewald equation and insulin was measured via radioimmunoassay.

6.3.3 Long Distance Corridor Walk

The LDCW was a 400 meter course which consisted of 10 laps along a hallway with cones set 20 meters apart (40 meters per lap). Participants were instructed to walk “at a pace that you can maintain for the full 10 laps.” Standard encouragement by trained staff was given at each lap. Heart rate was monitored with a Polar Pacer heart monitor (Model 60905; Woodbury, NY). Persons with elevated blood pressure (BP ≥200/110) or resting heart rate (>110 or <40) or reporting exacerbation of chest pain, shortness of breath, or cardiac event or procedure within the past three months were excluded for safety reasons. The LDCW was stopped if the participant’s heart rate exceeded 135 beats per minute (bpm) or if a participant reported chest pain or dyspnea during the test. Heart rate (HR) was recorded at rest before starting the walk, at completing, and at recovery 2 minutes later. Systolic blood pressure (SBP) was measured while seated prior to
the walk and standing at test completion. Based on these measures, cardiovascular (CV) response variables were generated. HR and SBP response were calculated by subtracting the resting values from those obtained immediately following completion. HR recovery was calculated by subtracting the HR obtained 2 minutes after LDCW completion from the value measured at completion. On average, the entire LDCW protocol takes approximately 8-10 minutes to administer.

6.3.4 Physical Activity Measures

Physical activity levels were assessed using both subjective and objective measurement tools. Physical activity was measured subjectively using a past year and past week version of the Modifiable Activity Questionnaire (MAQ) and objectively with the pedometer step counter.

In brief, the interviewer-administered, past year version of the Modifiable Activity Questionnaire (MAQ) questionnaire assesses current leisure and occupational activities, as well as extreme levels of inactivity due to disability (15). Physical activity levels were calculated as the product of the duration and frequency of each activity (in hours per week), weighted by an estimate of the metabolic equivalent (MET) of that activity and summed for all activities performed. Physical activity data were expressed as metabolic equivalent hours per week (MET hr-wk). The MAQ has been shown to be both a reliable (15, 16) and valid (15-17) assessment measure.

Physical activity was also assessed using a past week version of the MAQ. This questionnaire measures participation in leisure activities performed over the past 7 days. Study participants were given the past week MAQ during the eligibility visit and were asked to record
leisure activities for the 7 days prior to their clinic assessment. Past week leisure physical activity levels were calculated similar to that used for the leisure section of the past year MAQ.

At baseline, objective assessments of physical activity were obtained with the Accusplit Eagle AE120 (Accusplit Inc., Pleasanton, CA) pedometer in a subgroup of WOMAN study participants (n=170; 33.5%). The participants were instructed to wear the pedometer clipped to their waistband over the dominant hip for one week, and at the end of each day to record the number of steps taken in a diary. At the end of the week the participant returned the activity diary to the investigator. The number of steps recorded in the diary from the pedometer was averaged for the week to obtain a seven-day average of the number of steps taken per day.

6.3.5 Subclinical CVD Measures

Electron beam tomography, with an Imatron C-150 Scanner (Imatron, San Francisco, CA) was used to obtain 30-40 contiguous 3-mm-thick images of the heart, as previously described (18). Coronary artery calcification (CAC) scores were calculated according to the Agatston method. The reproducibility of the electron beam tomographic scans from this laboratory has an interclass correlation of 0.99 (18).

Detailed B-mode images of the right and left common carotid artery (CCA), carotid bifurcation, and the first 1.5 cm of the internal carotid artery (ICA) were obtained using a Toshiba SSA-270A ultrasound scanner (Toshiba America Inc., New York, New York) equipped with a 5-MHz linear array imaging probe. To measure the average intima-media thickness (IMT) of each segment, lines were electronically drawn along 1-cm segments of the lumen-intima interface and the media-adventitia interface of the near and far walls of the distal CCA.
and along the far walls of the carotid bulb and ICA. The average of these was recorded for each location. The mean of all average readings across the eight locations (four on each side) was calculated.

Stiffness of the aorta was measured using the gold standard, carotid-femoral (or aortic) pulse wave velocity (aPWV), as previously described in detail (19, 20). Briefly, for each participant, 20 seconds of carotid and femoral pulse waveforms were collected simultaneously with non-directional Doppler probes and recorded to data files. Files were “scored” using software developed by the Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging. For each file, the trained reader selected all clear waveforms for averaging into composite carotid and femoral waveforms, to determine the “foot” (or upstroke) of each. The transit time of the pulse wave was calculated as the foot-to-foot delay between the averaged carotid and femoral waveforms. The distance traveled by the pulse waveform between the carotid and femoral measurement sites was measured manually with a metal tape measure, above the surface of the participant’s torso. Aortic pulse wave velocity was calculated by dividing the distance traveled by the time differential between the two waveforms and was expressed as distance/transit time (cm/sec). Results from all usable data collection runs (n = 3) for each participant were averaged. In our lab this measure has been demonstrated to have good reproducibility with an intraclass correlation of 0.72-0.83 (19).

6.3.6 Statistical Methods

Univariate analyses were conducted on measured parameters from the LDCW, demographics, physical activity levels, and measures of subclinical CVD. Normally distributed variables were reported as mean ± standard deviation, non-normally distributed variables were reported as
median with 25th and 75th percentile, and proportions were noted for categorical variables. Spearman rank order correlation coefficients were used to assess the bivariate associations between walk time and CV response measures from the LDCW, demographics, physical activity levels, and CVD risk factors. Partial Spearman rank order correlations were used to further examine these relationships adjusted for age, age and BMI, and past year leisure physical activity levels. Descriptive statistics were used to illustrate demographics, physical activity levels, and CVD risk factors across quartiles of LDCW time. Depending upon the characteristics of the variable, ANOVA, Kruskal-Wallis, or Chi Square Test of Proportions was used to compare demographic factors, physical activity levels, clinical and subclinical CVD measures across quartiles of LDCW time in those who completed the 400-meter walk. Jonckheere-Terpstra tests were used estimate the linear trend in continuous variables and Cochran-Armitage Trend test were used to determine linear trend for categorical variables. Due to the high number of planned comparisons across quartiles of walk time, a p value of <0.002 will be used to denote statistical significance using the Bonferonni correction method.

### 6.4 RESULTS

Of the 508 women, 3 had missing walk time, 1 had an invalid walk time, and 1 woman did not complete the 10 laps due to elevated HR. Of those 503 (99%) women that completed the entire protocol, 11 (2%) had incomplete physical activity and/or coronary artery calcium (CAC) data and were excluded from the present analyses [8 of the 11 were missing past year leisure physical activity, 2 were missing past week leisure physical activity, and 1 woman had a missing CAC]
score]. The current report will focus on the remaining 492 WOMAN study participants with complete data.

At baseline, the mean age of the participants was 57.0 (range: 52 - 62.8) years, 11.8% were African American, and 59.4% (n = 292) reported taking HT at baseline. Study participants had a mean BMI of 30.8 (range: 23.3 – 41.3) kg/m² and waist circumference of 106.0 (range: 80.8 – 138.5) centimeters. Only 6.1% of women reported being current smokers at baseline. With regards to the measured parameters from the LDCW, on average the WOMAN study participants completed the walk in 301.2 seconds (approximately 5 minutes). Mean HR and SBP increased from resting by 36.8 bpm and 4.3 mmHg, respectively. At the end of the 2 minute recovery period, HR decreased by 20.4 bpm, which was approximately 55% of the HR response (Table 6.1).

Correlations between walk time and demographics, physical activity levels, CV response measures from the LDCW, and CVD risk factors are presented in table 6.2. Longer walk times were significantly (p<0.05) associated with older age and higher BMI and average WC levels. Walk time was inversely related to both subjective and objective assessments of physical activity levels as well as the CV response (HR and SBP) to the 400 meter walk. Longer walk times were related to higher resting HR and SBP, triglyceride, insulin, glucose, CAC score (continuous) and aPWV levels and lower HDL-C levels. The results were similar when the associations with walk time were adjusted for age alone (data not shown). However, when the results were adjusted for age and BMI, higher walk time was no longer significantly correlated with higher resting SBP, triglyceride, insulin levels or CAC score nor was walk time related to lower HDL-C levels. Adjusting for past year leisure physical activity levels did not substantially change the relationship between walk time and CVD risk factors (data not shown).
Table 6.3 describes the characteristics of the study population across quartiles of LDCW time. With regards to demographic factors, mean age, BMI, and WC significantly increased as time to complete the 400 meter course increased. In addition, the proportion of African American women was significantly higher in the slower walk time categories. The relationship between current HT use and walk time was not statistically significant. Regardless of whether activity was measured subjectively or objectively, median physical activity levels decreased across increasing walk time quartiles. Finally, relationships between walk time and CVD risk factors were investigated. The SBP and HR response to the LDCW and HR recovery decreased as mean walk time increased. Resting HR and SBP, LDL-C, insulin, and glucose levels increased as time to complete the 400 meter walk increased (significant at p<0.002 for resting HR, glucose, and insulin only). With regards to subclinical CVD measures, the proportion of detectable CAC (>0) was significantly higher among those with slower walk times. Median aortic PWV levels also significantly increased across increasing walk time quartiles. The association between walk time and IMT levels was not statistically significant.

6.5 DISCUSSION

In this large cohort of healthy postmenopausal women, 99% of study participants completed the LDCW testing protocol without complications. The high completion rate that was achieved in the current investigation confirms previous work suggesting that the LDCW protocol is practical to administer in large population studies. Furthermore, the significant trends that were observed between walk time and physical activity levels and measures of subclinical CVD indicate that the
LDCW has important psychometric properties among healthy, middle-aged, postmenopausal women.

In a practical sense, the LDCW protocol may be appealing in primary care settings due to the relative cost and time effectiveness, lack of required medical supervision, space and/or equipment, and patient familiarity of the activity mode (walking). Based on the findings from the current report, total walk time from the LDCW could be considered both a proxy measure for physical activity as well as an objective assessment of physical function and performance. The use of the LDCW protocol in clinical practice may allow health care providers to more effectively prescribe physical activity for their patients and/or monitor progress in healthy lifestyle based programs. In addition, when screening for CVD risk factors, poor performance during the LDCW could potentially identify those individuals who may warrant follow-up (cardiac) testing and evaluation.

In the current report, total walk time from the LDCW was inversely associated with physical activity levels as determined by the pedometer as well as past year and past week versions of the MAQ (15). Unlike past studies that estimated physical activity levels using subjective questionnaires, the present investigation also included an objective measure of physical activity, the pedometer step counter. Although subjective physical activity measures have been shown to accurately assess higher intensity, structured leisure physical activities, they typically do a poor job when measuring lower intensity, unstructured lifestyle physical activities, such as household chores, childcare, and housework (15, 21). In contrast, objective measures have the ability to capture both structured and unstructured activities thus providing a complete picture of an individual’s total physical activity levels (22). The decrease in physical activity levels that was observed across increasing walk times was similar regardless of the method that
was used to collect activity data (ie. subjective vs. objective assessment). Finally, when comparing the subjective activity assessments (past year vs. past week MAQ), the relationship with walk time was stronger with the past year measure as it may reflect more typical activity when compared to the past week estimate which may be subject to acute changes in health status.

When interpreting the findings of the present investigation, a number of limitations need to be considered. Data from only one point in time, the baseline visit, was used in the analyses. Although informative, this cross-sectional study analysis is limited in that it does not provide information pertaining to the direction of association or allow us to determine how the relationship between walking performance, physical activity, and CVD risk factors may change over time. In addition, maximal oxygen uptake (max VO$_2$) was not measured in the current investigation; therefore, the usefulness of the LDCW to estimate fitness levels in this population cannot be assumed. Finally, the ability to complete the LDCW and timed performance were found to be important prognostic factors for total mortality, CVD, and functional ability in older adults (7). Future work is needed to determine the predictive value of the LDCW for future morbidity and mortality in middle-aged, postmenopausal women.

As we move towards promoting physical activity for primary CVD prevention, quick and inexpensive tools are needed in order to ensure safe participation and/or evaluate progress in healthy lifestyle based programs. The evidence from the current report supports the utility of the LDCW to estimate the functional status of middle-aged, postmenopausal women. The information obtained during the LDCW protocol may allow health care providers to identify those individuals who may necessitate additional CVD screening.
**Acknowledgements:** The authors would like to acknowledge the contributions of the staff as well as the 508 dedicated participants of the WOMAN study. This research was funded by National Heart, Lung, and Blood Institute contract R01-HL-66468.


Table 6-1: Baseline Characteristics of the WOMAN Study Cohort (n=492)

<table>
<thead>
<tr>
<th>Corridor Walk Variables</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Corridor Walk Time, sec</td>
<td>301.2 (37.5)</td>
</tr>
<tr>
<td>HR at End of LDCW, bpm</td>
<td>107.0 (12.5)</td>
</tr>
<tr>
<td>SBP at End of LDCW, mmHg</td>
<td>128.5 (18.0)</td>
</tr>
<tr>
<td>2 Minute Recovery HR, bpm</td>
<td>86.6 (13.0)</td>
</tr>
<tr>
<td>SBP Response, mmHg</td>
<td>4.3 (13.1)</td>
</tr>
<tr>
<td>HR Response, bpm</td>
<td>36.8 (12.0)</td>
</tr>
<tr>
<td>2 Minute HR Recovery, bpm</td>
<td>20.4 (10.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Demographics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>57.0 (2.9)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.8 (3.8)</td>
</tr>
<tr>
<td>Average WC, cm</td>
<td>106.0 (11.3)</td>
</tr>
<tr>
<td>% African American</td>
<td>11.8%</td>
</tr>
<tr>
<td>% HS Education</td>
<td>98.6%</td>
</tr>
<tr>
<td>% Hormone Therapy Use</td>
<td>59.4%</td>
</tr>
<tr>
<td>% Current Smokers</td>
<td>6.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Activity Measures</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Past Year Leisure Activity, MET hr-wk</td>
<td>11.5 (5.2, 20.5)</td>
</tr>
<tr>
<td>Past Week Leisure Activity, MET hr-wk</td>
<td>11.2 (5.3, 19.3)</td>
</tr>
<tr>
<td>Pedometer, steps/day (n=170)</td>
<td>6446.9 (4801.4, 8721.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CVD Risk Factors</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting Heart Rate, bpm</td>
<td>70.2 (9.2)</td>
</tr>
<tr>
<td>Systolic Blood Pressure, mmHg</td>
<td>124.2 (16.3)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure, mmHg</td>
<td>76.8 (8.3)</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>216.4 (28.1)</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>128.0 (25.1)</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>60.0 (14.2)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>142.1 (74.3)</td>
</tr>
<tr>
<td>Insulin, mg/dL (n=432)</td>
<td>13.6 (6.7)</td>
</tr>
<tr>
<td>Glucose, mg/dL (n=486)</td>
<td>95.4 (9.3)</td>
</tr>
<tr>
<td>% Coronary Artery Calcification</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>49%</td>
</tr>
<tr>
<td>0-10</td>
<td>32.1%</td>
</tr>
<tr>
<td>11-100</td>
<td>13.6%</td>
</tr>
<tr>
<td>101+</td>
<td>5.3%</td>
</tr>
<tr>
<td>IMT (n=485)</td>
<td>0.71 (0.65, 0.76)</td>
</tr>
<tr>
<td>Pulse Wave Velocity, cm/sec (n=467)</td>
<td>846.2 (737.6, 988.8)</td>
</tr>
</tbody>
</table>

Normally distributed variables presented as mean (SD); non-normally distributed variables presented as median (25th, 75th percentile).
Table 6-2: Spearman Rank Order Correlations Between Walk Time from the Long Distance Corridor Walk (LDCW) and Related Factors

<table>
<thead>
<tr>
<th>Walk Time (sec)</th>
<th>Unadjusted</th>
<th>Adjusted for age and BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>0.13**</td>
<td>--</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>0.36****</td>
<td>--</td>
</tr>
<tr>
<td>Average WC</td>
<td>0.29***</td>
<td>--</td>
</tr>
<tr>
<td><strong>Physical Activity (PA) Levels</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past Year Leisure Activity</td>
<td>-0.23****</td>
<td>--</td>
</tr>
<tr>
<td>Past Week Leisure Activity</td>
<td>-0.18****</td>
<td>--</td>
</tr>
<tr>
<td>Pedometer Steps (n=170)</td>
<td>-0.25***</td>
<td>--</td>
</tr>
<tr>
<td><strong>Cardiovascular Response to LDCW</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP Response, mmHg</td>
<td>-0.13****</td>
<td>-0.22****</td>
</tr>
<tr>
<td>HR Response, bpm</td>
<td>-0.31**</td>
<td>-0.38****</td>
</tr>
<tr>
<td>HR Recovery, bpm</td>
<td>-0.44****</td>
<td>-0.48****</td>
</tr>
<tr>
<td><strong>CVD Risk Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting Heart Rate, bpm</td>
<td>0.17***</td>
<td>0.15***</td>
</tr>
<tr>
<td>Systolic Blood Pressure (BP), mmHg</td>
<td>0.10*</td>
<td>0.01</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>0.01</td>
<td>-0.04</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>0.08†</td>
<td>0.06</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>0.08†</td>
<td>0.06</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>-0.11**</td>
<td>-0.06</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>0.09*</td>
<td>0.04</td>
</tr>
<tr>
<td>Insulin, mg/dL (n=432)</td>
<td>0.26****</td>
<td>0.15**</td>
</tr>
<tr>
<td>Glucose, mg/dL (n=486)</td>
<td>0.13**</td>
<td>0.05</td>
</tr>
<tr>
<td>CAC</td>
<td>0.16***</td>
<td>0.01</td>
</tr>
<tr>
<td>IMT (n=485)</td>
<td>0.04</td>
<td>-0.04</td>
</tr>
<tr>
<td>Pulse Wave Velocity (n=467)</td>
<td>0.16***</td>
<td>0.12**</td>
</tr>
</tbody>
</table>

†<0.10; *p<0.05; **p<0.01; ***p<0.001; ****p<0.0001
Table 6-3: Characteristics of Study Participants by Quartiles of Walk Time (n=492).

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Quartile 1 (n=120)</th>
<th>Quartile 2 (n=123)</th>
<th>Quartile 3 (n=124)</th>
<th>Quartile 4 (n=125)</th>
<th>p value</th>
<th>p for linear trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>56.6 (2.8)</td>
<td>56.6 (3.0)</td>
<td>57.3 (2.9)</td>
<td>57.3 (2.8)</td>
<td>0.04</td>
<td>0.01</td>
</tr>
<tr>
<td>% African American</td>
<td>7.5</td>
<td>4.1</td>
<td>15.3</td>
<td>20</td>
<td><strong>0.0003</strong></td>
<td><strong>0.0002</strong></td>
</tr>
<tr>
<td>% Hormone Therapy users</td>
<td>43.3</td>
<td>31.7</td>
<td>42.7</td>
<td>44.8</td>
<td>0.14</td>
<td>0.42</td>
</tr>
<tr>
<td>Body Mass Index, kg/m²</td>
<td>29.3 (3.3)</td>
<td>30.1 (3.2)</td>
<td>30.7 (3.6)</td>
<td>32.9 (4.1)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average Waist Circumference, cm</td>
<td>102.4 (10.5)</td>
<td>104.1 (10.0)</td>
<td>106.7 (10.8)</td>
<td>110.5 (12.2)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical Activity (PA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past Year Leisure PA, MET hr-wk</td>
<td>15.7 (7.5, 27.0)</td>
<td>11.6 (5.5, 23.2)</td>
<td>10.6 (4.2, 17.5)</td>
<td>8.7 (4.0, 16.4)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Past Week Leisure PA, MET hr-wk</td>
<td>13.3 (7.7, 22.2)</td>
<td>11.7 (6.4, 22.6)</td>
<td>9.8 (5.0, 16.7)</td>
<td>9.9 (3.0, 15.5)</td>
<td>0.01</td>
<td>0.0007</td>
</tr>
<tr>
<td>Pedometer, steps/day</td>
<td>7285.2 (5670.7, 10427.6)</td>
<td>6523.1 (5112.1, 8686.7)</td>
<td>7132.5 (4864.6, 8426.4)</td>
<td>5482.3 (4204.3, 6581.4)</td>
<td>0.02</td>
<td>0.003</td>
</tr>
<tr>
<td>Cardiovascular Response</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic Blood Pressure (BP) Response, mmHg</td>
<td>6.4 (13.6)</td>
<td>4.6 (11.7)</td>
<td>4.0 (12.7)</td>
<td>2.5 (14.0)</td>
<td>0.14</td>
<td>0.0041</td>
</tr>
<tr>
<td>Heart Rate Response, bpm</td>
<td>42.6 (12.0)</td>
<td>37.3 (10.5)</td>
<td>34.6 (10.9)</td>
<td>32.9 (12.4)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart Rate Recovery, bpm</td>
<td>27.1 (9.6)</td>
<td>21.0 (9.8)</td>
<td>18.2 (8.8)</td>
<td>15.6 (9.0)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CVD Risk Factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart Rate, bpm</td>
<td>68.1 (9.3)</td>
<td>69.8 (8.3)</td>
<td>71.3 (9.5)</td>
<td>71.6 (9.3)</td>
<td>0.01</td>
<td><strong>0.0005</strong></td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>122.7 (13.2)</td>
<td>123.8 (13.8)</td>
<td>123.7 (13.5)</td>
<td>126.6 (13.8)</td>
<td>0.14</td>
<td>0.05</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>77.1 (8.0)</td>
<td>76.1 (8.7)</td>
<td>76.7 (7.7)</td>
<td>77.2 (8.8)</td>
<td>0.69</td>
<td>0.76</td>
</tr>
<tr>
<td>Total Cholesterol, mg/dL</td>
<td>213.1 (24.2)</td>
<td>215.5 (26.7)</td>
<td>218.5 (29.4)</td>
<td>218.5 (31.6)</td>
<td>0.36</td>
<td>0.08</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>124.3 (21.7)</td>
<td>127.7 (24.3)</td>
<td>129.1 (26.2)</td>
<td>130.9 (27.8)</td>
<td>0.22</td>
<td>0.0510</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>60.9 (13.8)</td>
<td>60.1 (13.7)</td>
<td>61.4 (14.5)</td>
<td>57.6 (14.7)</td>
<td>0.15</td>
<td>0.06</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>137.2 (75.5)</td>
<td>140.6 (79.2)</td>
<td>139.9 (72.1)</td>
<td>150.3 (70.3)</td>
<td>0.53</td>
<td>0.07</td>
</tr>
<tr>
<td>Insulin, mg/dL</td>
<td>12.0 (5.6)</td>
<td>11.7 (4.4)</td>
<td>14.4 (7.2)</td>
<td>16.1 (8.0)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>93.8 (7.6)</td>
<td>94.4 (8.3)</td>
<td>95.7 (9.5)</td>
<td>97.7 (11.0)</td>
<td>0.006</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>% Detectable CAC</td>
<td>40.8</td>
<td>51.2</td>
<td>49.2</td>
<td>62.4</td>
<td><strong>0.0008</strong></td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Intima Medial Thickness</td>
<td>0.70 (0.65, 0.77)</td>
<td>0.70 (0.65, 0.77)</td>
<td>0.70 (0.65, 0.75)</td>
<td>0.72 (0.65, 0.78)</td>
<td>0.62</td>
<td>0.48</td>
</tr>
<tr>
<td>Pulse Wave Velocity (cm/sec)</td>
<td>834.0 (721.7, 945.0)</td>
<td>843.3 (721.7, 945.0)</td>
<td>824.4</td>
<td>916.3</td>
<td>0.002</td>
<td>0.0009</td>
</tr>
</tbody>
</table>

Normally distributed variables presented as mean (SD); non-normally distributed variables presented as median (25th, 75th percentile).
Quartile 1: <267.6 seconds; Quartile 2: ≥ 267.6 to <305.4 seconds; Quartile 3: ≥ 305.4 to <319.2 seconds; Quartile 4: ≥ 319.2
Heart disease is the leading cause of death among American women. Overall, cardiovascular disease (CVD) claims the lives of more than ½ million women each year\textsuperscript{4}. Furthermore, nearly 2/3 of all CVD related deaths occur in women with no previous symptoms, making early detection and diagnosis particularly challenging in this population\textsuperscript{1, 2}. The present investigation focused on non-pharmacological strategies and inexpensive screening measures to facilitate effective primary CVD prevention in postmenopausal women.

7.1 SUMMARY OF FINDINGS

The findings from the current report confirm previous studies suggesting the overall benefit of physical activity, either separately or as part of a lifestyle intervention, on CVD risk factor reduction in postmenopausal women. However, previous investigations examining the beneficial role of physical activity and/or lifestyle intervention for primary CVD prevention have not adequately accounted for the added influence of HT, which is particularly relevant following the publication of the results from the Women’s Health Initiative (WHI) and Heart and Estrogen/progestin Replacement Study (HERS). The WOMAN study provided the unique opportunity to examine the separate and combined role of physical activity as part of a lifestyle intervention for CVD risk factor reduction by current and varying HT use (paper 1 and 2).
utility of the long distance corridor walk (LDCW) to estimate health status and as a crude measure of physical fitness was also examined using the WOMAN study cohort (paper 3). The specific findings from each of the three papers included in this report are provided in the following sections.

7.1.1 Paper 1

The purpose of paper 1 was to clarify the cross-sectional associations between leisure physical activity and lipids in postmenopausal women using specific lipoprotein subclass measures. In addition, paper 1 examined how current HT use may influence these relationships. Results of paper 1 suggested that baseline leisure physical activity levels were significantly associated with higher levels of HDL-C and large HDL-P, and lower levels of triglycerides, and total and medium VLDL-P, regardless of HT use. However, for several key lipoprotein subclass measures, the relationship with physical activity differed by HT use. After stratification by HT use, physical activity was independently related to larger mean HDL and LDL particle size, and lower levels of total and small LDL-P among non-HT users, but not among women currently taking HT.

7.1.2 Paper 2

The primary purpose of paper 2 was to determine the effectiveness of a lifestyle intervention to attenuate unfavorable CVD risk factor changes that were hypothesized to occur as result of HT discontinuation. In general, the lifestyle intervention was successful and had a positive impact on many CVD risk factors among both HT continuers and HT discontinuers. When compared to
the HE group, women randomized to the LC group increased leisure physical activity levels and improved saturated fat and cholesterol intake. Women in the intervention also made beneficial improvements with regards to a number of important CVD risk factors including weight, WC, insulin, glucose, and triglyceride levels. There were no significant differences at 18 months between randomized groups with regards to changes in HDL-C, systolic and diastolic blood pressure levels in either HT continuers or HT discontinuers.

In contrast, there was marked differences by randomized group assignment between HT continuers and HT discontinuers with regards to two key CVD risk factors; total cholesterol and LDL-C. When comparing total cholesterol and LDL-C change within the HE arm, women who had discontinued HT use had significantly higher increases in these two measures as compared to HT continuers. The significant differences in total and LDL cholesterol change between HT continuers and HT discontinuers were not replicated in the LC arm, suggesting that the lifestyle intervention successfully attenuated an increase in total cholesterol and LDL-C that likely would have occurred with HT discontinuation.

7.1.3 Paper 3

The purpose of paper 3 was to determine the utility of the long distance corridor walk (LDCW) in postmenopausal women. More specifically, paper 3 examined the associations between measured parameters from the LDCW and related factors such as physical activity subclinical CVD levels. Results from paper 3 suggested that walking performance was related to demographics factors such as age and race, anthropometric measures including BMI and WC, and physical activity levels. Walk time was also strongly related to detectable coronary artery calcification (CAC) as well as aortic pulse wave velocity (aPWV), both subclinical measures of
CVD, suggesting that the LDCW protocol is a useful, inexpensive measure among postmenopausal women using construct validity.

7.2 PUBLIC HEALTH SIGNIFICANCE AND CLINICAL IMPLICATIONS

In the post-WHI era, concern and confusion about the risks associated with HT has left women and their health care providers searching for safe and effective means to reduce CVD risk factors. There is a growing body of evidence to support that physical activity, and physical activity as part of a lifestyle intervention, is important for primary CVD prevention in women. However, prior to this report little was known regarding how the relationship between healthy lifestyles practices, more specifically physical activity, and CVD risk factors may be influenced by current (paper 1) or changing (paper 2) HT use. Data from the WOMAN study provided the unique opportunity to clarify these relationships. The public health significance and clinical implications that are specific to each of the three papers included in this report are provided in the following sections.

7.2.1 Paper 1

Paper 1 was the first to investigate the associations between lipids, physical activity, and hormone therapy (HT) using specific lipoprotein subclasses in postmenopausal women. The findings from paper 1 suggested that leisure physical activity was associated with favorable lipoprotein and lipid levels, regardless of HT use. However, some relationships were found to vary by HT. When the results were stratified by current HT use, physical activity was associated
with key lipoprotein subclasses in HT non-users which have been shown to be related to both incident and subclinical CVD. The results from paper 1 raise the important question as to whether the beneficial effect of physical activity on the lipid profile in postmenopausal women is similar between HT users and non-users. As HT is being prescribed less frequently and for shorter periods of time, we need to be aware of other strategies to favorably alter the overall lipid profile in postmenopausal women. Findings from this report suggested that the promotion of physical activity may be a safe and effective alternative to improve lipids and reduce risk of CVD in postmenopausal women.

7.2.2 Paper 2

At 18 months, we were able to examine the effectiveness of a lifestyle intervention for CVD risk factor reduction in postmenopausal women who were on HT at baseline and either continued or discontinued use. We were also able to investigate the additional benefit of lifestyle among women discontinuing HT (paper 2). A lifestyle intervention was shown to attenuate increases in total and LDL-C levels that resulted from HT discontinuation. In this era of uncertainty, one potential consequence of diminished HT use for CVD risk factor reduction is increased use of supplementary pharmacological agents, such as statins and aspirin; however, both are associated with side effects\textsuperscript{183, 184}. In addition, trial data suggests that aspirin does not protect women from CVD in a similar fashion to men\textsuperscript{185}. Furthermore, the majority of statin research to date has been conducted in men\textsuperscript{186, 187}. Based on the promising findings of paper 2, special attention should be paid to encouraging efficacious lifestyle strategies that are likely to convey more benefit and less risk than drug therapies. To date, few data was available regarding the widespread impact of the
WHI results on CVD risk factor change in postmenopausal women. The findings from the current report suggest that a lifestyle based approach is effective for general CVD risk factor reduction and can effectively attenuate negative changes to lipids that result from HT discontinuation.

7.2.3 Paper 3

As we move towards promoting physical activity in the community for primary CVD prevention, quick and inexpensive tools are needed to provide objective information regarding general functional and/or health status that would otherwise not be captured through subjective means. The findings presented in paper 3 supported previous efforts suggesting the practicality of the LDCW in large population studies. The direct relationship that was observed between walk time and subclinical CVD measures is particularly important and supports the utility of this measure in postmenopausal women. Based on these promising findings, the parameters measured during the LDCW may provide health care providers with additional, necessary information to appropriately ascertain CVD risk in apparently healthy, asymptomatic postmenopausal women.

7.3 LIMITATIONS

The WOMAN study provided the unique opportunity to investigate the role of lifestyle, including physical activity, for CVD risk factor reduction in postmenopausal women by varying HT use. However, several general limitations are applicable to all three papers and need to be considered when interpreting the findings from the current report.
1. **Hormone Therapy:** The WOMAN study participants were not randomized to HT use at baseline nor were they randomized to either continue or discontinue HT use at 18 months. Thus, the inability to randomize the HT component of the WOMAN study may influence the findings of papers 1 and 2.

2. **Study Population:** The WOMAN study cohort consisted primarily of healthy, well-educated, Caucasian women. Thus, the results from the current investigation may not be generalizable to women of lower socio-economic status and/or women representing minority populations.

3. **Study Design:** The WOMAN study was also not designed to investigate the independent contributions of the specific intervention components for CVD risk factor reduction. Therefore, the independent effect of physical activity, diet, and/or weight loss on CVD risk factors would be difficult to separate out from the overall effect of the lifestyle intervention.

4. **Sample Size:** A larger and more diverse study cohort would have provided more statistical power to perform more detailed subgroup analyses.

5. **Assessment of Physical Activity:** Although both subjective and objective physical activity assessments were included in the WOMAN study, the findings from the current report were based primarily from leisure physical activity estimates obtained from the past year version of the Modifiable Activity Questionnaire (MAQ)\(^{144}\). Self-reported physical activity estimates are subject to response bias which may influence the precision in measures of physical activity and related energy expenditure\(^{188,189}\). While subjective measures accurately assess moderate to higher intensity activities, focusing
solely on higher intensity activities may not be valid among women who may acquire
the bulk of their physical activity in lower intensity activities\textsuperscript{144, 190}. Thus, the lack of
incorporating the objective measure of physical activity (pedometer) into the analyses
may affect the findings of paper 1 and 2.

The limitations that are specific to each of the three papers included in this report are provided in
the following sections:

\subsection*{7.3.1 Paper 1}

When interpreting the findings from paper 1, a number of limitations need to be considered. Data from only one point in time, the baseline visit, was used in the analyses. Although informative, this cross-sectional study analysis is limited in that it does not provide information pertaining to the direction of association or allow us to determine how the relationship between physical activity and lipoprotein subclasses changes as a woman changes her physical activity levels, HT status, or both. In addition, the results were adjusted for lifestyle factors (age, BMI, dietary saturated fat and cholesterol intake) that have been demonstrated to be related to both physical activity and lipid and lipoprotein subclass levels. Finally, women were classified as current HT users or non-users; the type, dosage, and/or duration of HT usage were not considered in these analyses.

\subsection*{7.3.2 Paper 2}

The limitations of paper 2 should also be recognized. Given that this was a behavioral intervention, there may be a differential reporting bias with the intervention group reporting what
they should have been doing rather than what they were actually doing. For the purposes of paper 2, women were classified as HT continuers or HT discontinuers at 18 months; therefore, the duration of prior HT usage and/or time since discontinuation were not considered in these analyses. Finally, saturated fat and cholesterol intake was used as general measure of diet composition; therefore, other diet quality data was not considered in these analyses.

7.3.3 Paper 3

Paper 3 was a cross-sectional investigation and was; therefore, subject to the same study design limitations that were previously described for paper 1. In addition, VO\textsubscript{2} max, the current gold standard for assessing cardiovascular fitness, was not measured in this population. Therefore, the validity (convergent) of the LDCW to estimate fitness levels cannot be assumed. Finally, the LDCW was a tool developed to assess fitness levels and physical function in an older population. In younger individuals the time taken to complete the 400 meter course may be overestimated due to the fact that those walking at higher speeds may need to slow down in order to navigate around turns. In a previous investigation, it was suggested that walk time was not accurate in estimating peak VO\textsubscript{2} in individuals who walked at speeds of 3.75 mph (<240 seconds) and higher\textsuperscript{172}. However, it should be noted that only two of the 492 (0.4%) women included in the present investigation completed the test protocol in less than 240 seconds.
7.4 FUTURE RESEARCH

The limitations that were identified in the previous section can be used to guide future research efforts. Although the WOMAN study cohort included women representing minority populations, 88% of the participants were of Caucasian descent. In addition, over 98% had achieved at least a high school degree, indicating that the cohort was of higher socio-economic status. Therefore, future efforts need to focus on translating the WOMAN lifestyle intervention into more diverse community settings with less manpower and a smaller budget. Future work should also examine whether total physical activity levels, including both structured and unstructured activities as measured by an objective assessment tool, follows the same trends as what was observed in the current report. An objective measure of physical activity would also provide the opportunity to validate the activity estimates that were obtained via subjective questionnaires. Finally, the ability to complete the LDCW and timed performance were found to be important prognostic factors for total mortality, CVD, and functional ability in older adults. Future work is needed to determine the predictive value of the LDCW for future morbidity and mortality in middle-aged, postmenopausal women.

7.5 CONCLUSION

In the current report, strategies for primary CVD prevention in postmenopausal women were examined. At baseline, leisure physical activity levels were shown to be beneficially related to improved lipid and lipoprotein subclass levels with many of these associations influenced by current HT use. Physical activity, as part of a lifestyle intervention, was also shown to be
effective for general CVD risk factor reduction regardless of HT continuation or discontinuation at 18 months. In addition, the lifestyle based intervention attenuated increases in total and LDL-C levels that apparently resulted from HT discontinuation. Finally, findings from the current report also suggested that a simple test of walking endurance may provide supplemental information when ascertaining CVD risk in women.

In conclusion, the development of primary CVD prevention strategies to decrease the burden from incident CVD in women has important public health implications. Currently, there is much concern and confusion about the risks associated with HT use and discontinuation of use. The findings from the current report suggest that a non-pharmacological, healthy lifestyle approach for CVD risk factor reduction is a safe and effective strategy for primary CVD prevention in healthy, middle-aged, postmenopausal women.
APPENDIX A: WOMAN STUDY PARTICIPANT INFORMATION FORM
WOMAN Study

Participant Information

Please only complete lines where there are changes from last visit.

ID: ______________

Date: _____/____/____ (MM/DD/YY)

Staff: ______________

Name: ____________________________________________________________

Address: __________________________________________________________

_________________________________________________________________

Phone #: (Home) (___)__________________________

(Work) (___)__________________________

(Other) (___)__________________________

Email: ____________________________

Alternative Contact: _____________________________ Phone (Home): (___)________

(Preferably somebody who does not live with you)

Relation to Participant: ____________________________ (Work): (___)________

Emergency Contact: _____________________________ Phone (Home): (___)________

Relation to Participant: ____________________________ (Work): (___)________

Primary Physician’s Name: ____________________________________________

Address: __________________________________________________________

_________________________________________________________________

PCP Phone #: (___)_______________________________
ID ____________  
Date___________  

The WOMAN on the Move Study

HEIGHT, WEIGHT, AND WAIST MEASUREMENTS:

1. **Standing Height**- Record to nearest half-inch (round up) without shoes:  
   _____. ____ inches  
   _____. ____ cm
2. **Weight** - record to nearest half-pound, (round up) clothed, without shoes:  
   _____. ____ lbs.  
   _____. ____ kg.

WAIST MEASUREMENTS (cm) - Record to nearest (.1) cm  
1st reading_____________  
2nd reading_____________  
3rd reading_____________  

If first 2 readings are within 2 cm, average the 2. If not, do a third measurement and average the 2 measures within range (2 cm). If even after 3 measures there are no matches, take the average of the 2 closest measurements.

3. Average waist circumference _____. ____ cm  
   (> 80 cm – eligible)

HEART RATE  
4. Beats in 30 seconds: ________X2 = _________

BLOOD PRESSURE MEASUREMENTS:

Cuff Size: _____ Regular  
_____ Large  
_____ Pediatric  
_____ Thigh  
Arm: _____ Left  
_____ Right

5. First Reading __________/__________  
   Systolic  
   Diastolic
6. Second Reading __________/__________  
   Systolic  
   Diastolic
7. Average of blood pressure Readings __________/__________  
   Systolic  
   Diastolic
BLOOD DRAW (12 HOUR FAST)

8. When did you last have anything other than water to eat or drink? ________ a.m./p.m.

Note: If less than 10 hours from clinic appointment, participant should be rescheduled for the blood draw.

Time Blood Drawn: __________ a.m./p.m.

Difficult blood draw? 1. □Yes  2. □No

Was blood sample collected? 1. □Yes  2. □No, specify reason

Tubes collected: (✔ if completed)
    EDTA 10mL: ______
    Serum 15 mL: ______
    Serum 10 mL: ______
    Na Nitrate 5mL: ______

MEDICATION(S) LIST

9. Over the past 2 weeks have you taken any prescribed medications?
   1. □Yes  2. □No

Medication 1:         Medication 2:         Medication 3:
Type _______________ Type _______________ Type _______________
Date began ______ mo/yr Date began______ mo/yr Date began______ mo/yr
Dose _____________ mg Dose _____________ mg Dose _____________ mg
Freq. ______________ x /day Freq. ______________ x /day Freq. ______________ x /day
Reason ________________ Reason ________________ Reason ________________

Medication 4:         Medication 5:         Medication 6:
Type _______________ Type _______________ Type _______________
Date began ______ mo/yr Date began______ mo/yr Date began______ mo/yr
Dose _____________ mg Dose _____________ mg Dose _____________ mg
Freq. ______________ x /day Freq. ______________ x /day Freq. ______________ x /day
Reason ________________ Reason ________________ Reason ________________
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<thead>
<tr>
<th>Medication 7:</th>
<th>Medication 8:</th>
<th>Medication 9:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type:</td>
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<td>Date began:</td>
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<tr>
<td>Reason:</td>
<td>Reason:</td>
<td>Reason:</td>
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</table>

9a. Do you take aspirin (not Tylenol):  
(0) □ daily  
(1) □ 1-6 times/week  
(2) □ less than once/week  
(3) □ rarely  
(4) □ never (go to blood results)  

9b. When you take aspirin, how many on the average do you take per day? ______ per day  

9c. How many aspirin have you taken in the last 48 hours ______ aspirin  
(00 if none)  

**HORMONE REPLACEMENT USE**  
10. Are you currently taking hormone therapy?  
(1) □ Yes (if yes, proceed to #11)  
(2) □ No  

10a. If no, what was the date that you stopped taking HRT? ______ (MM/YY) (proceed to #13)  

11. What are the hormones that you are taking?  

<table>
<thead>
<tr>
<th>Hormone 1: (Please circle one)</th>
<th>Hormone 2: (Please circle one)</th>
<th>Hormone 3: (Please circle one)</th>
<th>Hormone 4: (Please circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Patch Injection Other</td>
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<td>Name</td>
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<td>Date Began (MM/YY)</td>
<td>Date Began (MM/YY)</td>
<td>Date Began (MM/YY)</td>
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<td>Months Taken</td>
<td>Months Taken</td>
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<td>Months Taken</td>
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</table>
12. Have you stopped taking your hormones in the past year for more than 1 week?
   1. □ Yes  2. □ No ⇒ Go to #14
      a. If yes, how many occasions did you stop taking your hormones? _____ (Proceed to #14)

13. What were the primary reasons you stopped taking hormone replacement therapy? (Check all that apply)
   □ Directed by physician
   □ Needed second opinion from another doctor
   □ Felt like I didn’t need it
   □ Thought the medication was harmful
   □ The cost of the medication
   □ Developed a new health problem
   □ Heard about the Women’s Health Initiative HRT results and decided to stop because of health risks
   □ Had undesirable side effects (check all that apply below):
      ___ Weight gain ___ Depression/mood swings
      ___ Bleeding ___ Flu-like symptoms
      ___ Breast lumps ___ Headaches
      ___ Breast tenderness ___ Other_________________
   □ Other (please specify)________________________________________

14. Have you experienced any side effects while on HRT?
   1. □ Yes  2. □ No
      (if yes, check all that apply below)
      ___ Weight gain ___ Depression/mood swings
      ___ Bleeding ___ Flu-like symptoms
      ___ Breast lumps ___ Headaches
      ___ Breast tenderness ___ Other_________________

15. Do you currently smoke?
   1. □ Yes  2. □ No

16. Have you had a mammogram in the last year?
   1. □ Yes  2. □ No  1a. If yes, Date: _____/_____/yr
      If no, explain importance of mammography and where to have them done

17. Have you ever been diagnosed by a physician with cancer?
1. □ Yes 2. □ No (If no, proceed to #18)
   17a. If yes, Date: _____/_____mo/yr

   17b. If yes, which type?
       □ Breast
       □ Uterine (Endometrium)
       □ Ovary
       □ Other, describe ____________

18. Have you had a cardiovascular event since the start of your participation in this study?
   1. □ Yes 2. □ No (If no, questionnaire, go to #19)

   18a. If yes, which type of event?
       □ Myocardial infarction; Date:_____/_____mo/yr
       □ Stroke; Date:_____/_____mo/yr
       □ Venous thrombosis: Date:_____/_____mo/yr
       □ Aneurysm, in what location (e.g., aortic)?__________; Date:_____/____mo/yr
       □ Other?, describe_________________________; Date:_____/______mo/yr

19. Has your doctor ever told you that you have:
    Arthritis 1. □ Yes 2. □ No
    Diabetes (Sugar) 1. □ Yes 2. □ No
    Lung Disease 1. □ Yes 2. □ No
    Kidney Disease 1. □ Yes 2. □ No
    Pancreatitis 1. □ Yes 2. □ No
    Gallstone 1. □ Yes 2. □ No
    Thyroid Disease 1. □ Yes 2. □ No

20. Have you ever had gastric bypass surgery?
    1. □ Yes 2. □ No

    If yes; Date:_______/________mo/yr
Corridor Walk

Exclusion Questions

Script: “The following tests will assess your physical fitness by having you walk 1/4 mile at a steady pace. First I need to ask you a few questions to see if you should try the test.”

a. Does the participant use a walking aid, such as a cane?  
   Yes  No

b. Within the past 3 months, have you had a heart attack?  
   Yes  No

c. Within the past 3 months, have you had angioplasty?  
   Yes  No

d. Within the past 3 months, have you had heart surgery?  
   Yes  No

e. Within the past 3 months, have you had any new or worsening heart pain or angina?  
   Yes  No

Demonstration

a. Attachment for heart rate monitor:  
   Script: “This device measures your pulse, or how often your heart beats.”

400-Meter Walk Test Performance

Script: “You will be walking 10 complete laps around the course, about 1/4 mile. We would like you to walk at a normal pace you can maintain over the 10 laps. After you complete the 10 laps I will tell you to stop, and measure your blood pressure and heart rate. “STOP” symptoms Script: “Please tell me if you felt any chest pain, tightness or pressure in your chest, if you become short of breath or if you feel faint, lightheaded, or dizzy, or if you feel knee, hip, calf, or back pain. If you feel any of these symptoms, you may slow down or stop. Do you have any questions?”. (Start walking when I say ‘GO’ and try to complete 10 laps at a pace you can maintain. Ready, go.)

a. Baseline heart rate:  
   ___________ bpm

b. Cross off as each lap is completed:  
   1 2 3 4 5 6 7 8 9 10

c. Number of laps completed:  
   ___________ laps

d. Did participant complete all 10 laps  
   1. Yes  2. No

e. Record time at 400m or at stop:  
   ____ : ___ . ___  
   (Min:sec.hundredths/sec)
f. Did the heart rate exceed 135 bpm at any time during the 400-meter walk?  
1. Yes  2. No

g. Heart rate at 400m or at stop:  _____________ bpm

h. Blood pressure at 400m or at stop:  ______/______ mmHg

i. Heart rate **2 minutes** after completion of 400m walk:  _____________ bpm

j. Did the participant complete the 400-meter walk?  
1. Yes  2. No

**Reason walk was incomplete or not done:**  
Excluded based on criteria  
Refused  
Heart rate > 135 bpm during 2-minute walk  
Heart rate < 40 bpm  
Symptoms reported during walk:  
*Specify reason*  
Stopped by technician:  
*Specify reason*  
Other:  
*Specify reason*

While you were walking, did you have any of the following symptoms?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Yes</th>
<th>No</th>
<th>Don’t Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest pain?</td>
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<td>Shortness of breath?</td>
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<td>Knee pain?</td>
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<td>Hip pain?</td>
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<td>Calf pain?</td>
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<td>Foot pain?</td>
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<tr>
<td>Numbness or tingling in your legs or feet?</td>
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<td>Leg cramps?</td>
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<td>Back pain?</td>
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<tr>
<td>Other symptoms*?</td>
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</table>

*Please specify: ____________________________________________________________

*Please specify: ____________________________________________________________
APPENDIX B: WOMAN STUDY PHLEBOTOMY FORM
WOMAN Phlebotomy/Processing Form

DATE__________ Phlebotomist ID: _______ ID: ____________

PHLEBOTOMY

Participant Questions:
1. Do you bleed or bruise easily?
   No: _______ Yes: _______ Don’t Know: ______
2. Have you ever been told you have a disorder related to blood clotting or coagulation?
   No: _______ Yes: _______ Don’t Know: ______
3. Have you ever experienced fainting spells while having blood drawn?
   No: _______ Yes: _______ Don’t Know: ______
4. Do you have diabetes?
   No: _______ Yes: _______ Don’t Know: ______
5. Are you fasting?
   No: _______ Yes: _______ If yes, how long?

Was any blood drawn: (circle one) Yes No
Time Drawn: _______________
If no, reason not drawn: ________________________________________________

Venipuncture:
Venipuncture time elapsed: _______________ minutes
Time elapsed until tourniquet released: _______________ (2 min optimum)
Quality of venipuncture: C (Clean) T (Traumatic - please specify)
A. Vein collapse B. Hematoma C. Vein Hard to get D. Multiple sticks
   E. Excessive duration of draw F. Leakage at venipuncture site
Site of venipuncture:
Position of participant during blood drawing: supine sitting

Blood drawing:
Blood Volume per Tube: Fill (✓) Other (specify volume)
1. EDTA 10mL
2. Serum 15mL
3. Serum 10mL
4. Na citrate 5mL
5. Li Heparin 4mL

PROCESSING

Processor ID: ________________
Centrifuge after 30 minutes:
Indicate after centrifugation complete whether plasma is Lipemic (L), Icteric (I), Hemolyzed (H), or clotted (C).
Tube (✓) * Lab Number vol(ml) Suggested Aliquot Blind
done Dupl. (✓) Comment
#1 NMR EDTA ( ) L 2mL Cryovial ( )
#2 DNA EDTA ( ) S 1mL Cryovial ( )
#3 Extra EDTA ( ) S 1mL Cryovial ( )
#4 Extra EDTA ( ) S 1mL Cryovial ( )
#5 Na citrate ( ) V 1mL Cryovial ( )
#6 Na citrate ( ) V 1mL Cryovial ( )
#7 Serum ( ) H 3mL Cryovial ( )
#8 Serum L(a) ( ) H 1mL Cryovial ( )
#9 Serum CRP ( ) V 1mL Cryovial ( )
#10 Serum IL-6 ( ) V 1mL Cryovial ( )
#11 Serum Est. Met.( ) I 1mL Cryovial ( )
#12 Serum TSH ( ) I 1mL Cryovial ( )
#13 Extra Serum( ) S 1mL Cryovial ( )
#14 Extra Serum( ) S 1mL Cryovial ( )

*L=Lipomed V=University of Vermont H=Heinz Lab S=Storage

Received Date: ________________ Time: ________________ Frozen: ________________
Comment: __________________________________________________________________

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APPENDIX C: WOMAN STUDY PHYSICAL ACTIVITY MEASURES
**THE MODIFIABLE ACTIVITY QUESTIONNAIRE (MAQ)**

1. Please circle all activities listed below that you have done more than 10 times in the past year from ________________ to ________________.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Activity #</th>
<th>JAN</th>
<th>FEB</th>
<th>MAR</th>
<th>APR</th>
<th>MAY</th>
<th>JUN</th>
<th>JUL</th>
<th>AUG</th>
<th>SEPT</th>
<th>OCT</th>
<th>NOV</th>
<th>DEC</th>
<th>Average # of Times per Month</th>
<th>Average # of Months Each Time</th>
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<tr>
<td>Jogging (outdoor, treadmill)</td>
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<td>Swimming (laps, snorkeling)</td>
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<td>Bicycling (indoor, outdoor)</td>
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<td>Softball/Baseball</td>
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<td>Volleyball</td>
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<td>Bowling</td>
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<td>Skating (roller, ice, blading)</td>
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<td>Martial Arts (karate, judo, kendo)</td>
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<td>Calisthenics/Toning Exercises</td>
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<td>Wood Chopping</td>
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<td>Elliptical Trainer</td>
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<td>Walking for Exercise (outdoor, indoor at a mall or fitness center, treadmill)</td>
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<td>14 Football/Socer</td>
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<td>15 Raquetball/Squash</td>
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<td>16 Horseback Riding</td>
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<td>19 Aerobic Dance/Step Aerobic</td>
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<td>20 Water Aerobics</td>
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<tr>
<td>21 Dancing (square, line, ballroom)</td>
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<td>22 Gardening or Yardwork</td>
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<tr>
<td>23 Badminton</td>
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<tr>
<td>24 Strength/Weight Training</td>
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<td>32 Canoeing/Rowing Kayaking</td>
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<td>33 Water Skiing</td>
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<td>34 Jumping Rope</td>
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<td>35 Snow Skiing (x-country)</td>
<td>35</td>
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<td>36 Snow Skiing (downhill)</td>
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<td>37 Snow Shoeing</td>
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<td>38 Yoga</td>
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<td>39 Other</td>
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<tr>
<td>40 Walking for Exercise (outdoor, indoor at a mall or fitness center, treadmill)</td>
<td>40</td>
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</tbody>
</table>

List each activity that you circled in the “activity” box below, check the months that you did each activity over the past year and then estimate the average amount of time spent in that activity. If participant did not participate in any activities, please check the box below marked none.

None ☐

2. Excluding time at work, in general how many HOURS per DAY do you usually spend watching television or walking on the computer? ________ hours

3. Over this past year, have you spent more than one week confined to a bed or chair as a result of an injury, illness, or surgery? Yes _______ No _______
   If yes, how many weeks over the past year were you confined to a bed or chair? ________ weeks

4. Do you have difficulty doing any of the following activities?
   a. getting in or out of a bed or chair? Yes _______ No _______
   b. walking across a small room without resting? Yes _______ No _______
   c. walking for 10 minutes without resting? Yes _______ No _______
5. Did you ever compete in an individual or team sport (not including any time spent in sports performed during school physical education classes)?  Yes _______  No _______  
   If yes, how many total years did you participate in competitive sports? _______ years

6. Have you had a job for more than one month over the past year, from last _____ to this_____?

List all JOBS that the individual held over the past 12 months for more than one month. 
Account for all 12 months of the past year. IF unemployed/disabled/homemaker/student during all or part of the past 12 months, list as such and probe for job activities of a normal 8 hour day, 5 day week.

<table>
<thead>
<tr>
<th>Job Name</th>
<th>Job Code</th>
<th>Walk or bicycle to/from work</th>
<th>Average Job Schedule</th>
<th>Hrs, spent sitting at work</th>
<th>Check the category that best describes job activities when not sitting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Min/Day</td>
<td>Mos/Yr</td>
<td>Days/Wk</td>
<td>Hrs/Day</td>
</tr>
</tbody>
</table>

**Category A**
(Includes all sitting activities)

- Sitting
- Standing still w/o heavy lifting
- Light cleaning
- Driving a bus, taxi, tractor
- Jewelry making/weaving
- General Office Work
- Occasional/short distance walking

**Category B**
(Includes most indoor activities)

- Carrying light loads
- Continuous walking
- Heavy cleaning
- Gardening
- Painting/Plastering
- Plumbing/Welding
- Sheep Herding

**Category C**
(heavy industrial work, outdoor construction, farming)

- Carrying moderate to heavy loads
- Heavy construction
- Farming
- Digging ditches, shoveling
- Chopping (ax), sawing wood
- Tree/pole climbing
- Water/Coal/Wood Hauling

**JOB CODES**

Seven Day
Physical Activity Diary

ID______________________

Dates Recorded
_____ / _____ / _____ to
_____ / _____ / _____

Phone (____)______________
Reviewer Initials __________
Directions

Please complete your log the week following your clinic visit. This log consists of two parts 1). the pedometer and 2). activity diary. We are asking you to wear the pedometer and record your activities every day for a full seven-day period. For each of the seven days, please check the day of the week (ex. Monday) and write in the date. Each of the seven days is to be recorded on a separate sheet.

Pedometer Instructions: The monitor is to be clipped snugly to your clothes or on a belt at the waist. First thing every morning, just before you put on the monitor, push the reset button and make sure the monitor reads “zero”. Record the time you put on the monitor in your activity log and circle am or pm. Keep the monitor on all day, except when swimming or bathing. Remove the monitor at night just before bedtime and record the number of steps per day along with the time that it was removed in the activity log and circle am or pm. Please repeat these steps for the next seven days.

Activity Diary Instructions: Only include activities or exercises you do for 10 minutes or longer*. Please include only the time that you are actually active. Examples of physical activity includes brisk walking, gardening or yardwork, aerobics, swimming, stairclimbing, dancing, golf, weight training, etc. List each activity that you did during the day as well as the amount of time you spent doing that particular activity.
Day 1:

☐ Sunday  ☐ Monday  ☐ Tuesday  ☐ Wednesday  ☐ Thursday  ☐ Friday  ☐ Saturday

Date: __ __ / __ __ / __ __

Time you put the monitor on in the morning: __ __ : __ __ am or pm

Time you took the monitor off in the evening: __ __ : __ __ am or pm

The number of steps taken today from the pedometer: ________________

Did you remove the monitor for longer than 30 minutes for any reason today such as bathing, swimming, or water aerobics? If YES, please fill in the time that the monitor was taken off and the time it was put back on.

<table>
<thead>
<tr>
<th>Activity</th>
<th>YES</th>
<th>NO</th>
<th>Time Monitor Removed</th>
<th>Time Monitor Put Back On</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bathing</td>
<td>☐</td>
<td>☐</td>
<td>__ __ : __ __ am or pm</td>
<td>__ __ : __ __ am or pm</td>
</tr>
<tr>
<td>Swimming/Water Aerobics</td>
<td>☐</td>
<td>☐</td>
<td>__ __ : __ __ am or pm</td>
<td>__ __ : __ __ am or pm</td>
</tr>
</tbody>
</table>

**Leisure Physical Activity Done Today for 10 minutes or more**

<table>
<thead>
<tr>
<th>Activity/Exercise</th>
<th>Total Minutes/Day</th>
<th>Activity Code</th>
</tr>
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<tbody>
<tr>
<td>WALKING</td>
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<td>6.</td>
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*NOTE: This form is replicated for an additional 6 days to obtain 7 days of pedometer step counts and reported leisure physical activity levels.*
APPENDIX D: WOMAN STUDY DIETARY MEASURES
CONNOR DIET HABIT SURVEY

Meat, Fish, and Poultry
Consider your eating habits during the last month. For each question, circle all numbers that apply.

1. Which type of ground meat do you usually eat?
   1. Regular hamburger (30% fat)
   2. “Lean” ground beef (25-27% fat)
   3. Ground chuck (20% fat)
   4. Ground round or ground sirloin, other than Giant Eagle’s ground sirloin, ground turkey (15% fat)
   5. “Extra lean”, “Ultra lean” or “93/7” (4-10% fat), Giant Eagle’s ground sirloin (7-10% fat), ground turkey breast, ground chicken breast
   6. Eat no ground meat

2. Which best describes your typical lunch? “Lunch meat” means ham, bologna, salami, pastrami, etc.
   1. Cheeseburger, pizza, typical cheeses, egg dishes (egg salad, quiche, frittata, etc.)
   2. Sandwich (regular lunch meat, hamburger, grilled cheese), meat/fried chicken entrée, regular hot dog
   3. Skip lunch or sandwich (tuna, fish, peanut butter, chicken or turkey lunch meat/light mayo, etc), turkey hot dog, vegetarian dishes
   4. Tuna sandwich (w/mayo: 1 gm fat or less/Tbsp), veggie burger (e.g. Harvest, Garden, Boca), entrée (fish [not fried], small bits of chicken or meat), low-fat yogurt
   5. Salad (low cal dressing), low-fat vegetarian dishes, low fat or fat-free hot dog (0-2 gm fat), deli meats/fat free sandwich (w/mayo: 1 gm fat or less/Tbsp), bagel (light cream cheese)
   6. Fat free vegetarian dishes, salad (fat free dressing), veggie dog, garden vegan (fat free soy burger), nonfat yogurt, dry cereal (skim milk), bagel (fat free cream cheese)

3. Circle all of the choices that reflect your entrée at your main meal.
   1. Cheese (cheddar, jack, etc.), eggs, organ meats (liver, etc), pizza, regular (not low fat) vegetarian dishes once a week or more.
   2. Beef, lamb, pork, or ham once a week or more
   3. Very lean red meat (top round or flank steak), rabbit, veal, or venison once a week or more
   4. Chicken, turkey, crab, lobster or shrimp twice a week or more
   5. Fish, scallops, oysters, clams, low-fat vegetarian dishes twice a week or more
   6. Fat free vegetarian dishes, fat free seafood dishes every day

4. Estimate the number of ounces of meat, cheese, fish and poultry you eat in a typical day. Include all meals and snacks.
   To guide you in your estimate (a piece the size of a deck of cards = 3 oz)
   1 hot dog = 1 ½ oz
   4 strips of bacon = 1 oz
   1 sm. burger patty = 3-4 oz
   1 slice cheese = 1 oz
   1 chicken thigh = 2-3 oz
   ½ chicken breast = 3 oz
   average T-bone steak = 8 oz
   1-inch cute cheese = 1 oz
   most sandwich meat = 2-3 oz
   1. eleven or more ounces a day
   2. nine to 10 ounces a day
   3. six to 8 ounces a day
   4. four to 5 ounces a day
   5. up to 1 ounce cheese or 3 oz lean meat, poultry, shrimp, crab, lobster or 6 oz fish, clams, oysters, scallops a day
   6. none or up to 3 oz shrimp, crab, lobster or 6 oz fish, clams, oysters, scallops a day
5. Which of these have you eaten in the past month?
   1. bacon, sausage
   2. Canadian bacon, turkey, or chicken sausage
   4. vegetarian sausage (e.g. Morningstar links or patties, other soy sausage)
   6. none

Dairy Products and Eggs
Consider your eating habits during the last month.
For each question, circle all numbers that apply

6. Which do you usually use for drinking (don’t forget lattes/mochas) or cooking? (most lattes/mochas contain whole milk unless you request otherwise).
   1. whole milk
   2. two percent milk
   4. one percent milk, buttermilk, nondairy beverages (edensoy, rice dream, etc)
   5. none or skim (non-fat) milk, light nondairy beverages (edensoy light, rice dream light, etc)

7. Which toppings do you use?
   1. sour cream (real or imitation), whipped cream
   2. light/lowfat sour cream, cool whip, reddi-whip aerosol dairy topping
   3. cool whip light, regular cottage cheese, whole milk yogurt
   4. low fat yogurt, 2% lowfat cottage cheese, reddi-whip aerosol nondairy
   5. 1% fat cottage cheese, cool whip free, soy yogurt
   6. none or nonfat sour cream, nonfat yogurt, nonfat cottage cheese

8. Which frozen desserts are you most likely to eat at least once a month?
   1. ice cream (5 to 18 g fat per ½ cup)
   2. light ice cream (4 g fat per ½ cup)
   3. ice milk, most soft ice cream, frozen yogurt (cream added), tofu
   4. sherbet, lowfat frozen yogurt, soy delicious
   5. none or nonfat frozen yogurt, sorbets, popsicles

9. Which kind of cheese do you use?
   2. cheddar, swiss, jack, brie, feta, montrachet, blue, jarlsberg, whole milk mozzarella, Neufchatel or regular cream cheese, processed cheese (velveeta, American, cheese whiz), kraft deluxe slices, parmesan
   6. part skim mozzarella, light cream cheese, light cheddar, light jack, (kraft light naturals, alpine lace-lo, velveeta light, or other part-skim cheeses), string cheese
   8. jarlsberg light, athenos reduced fat feta cheese, 2% milk processed cheese slices
   10. light part skim mozzarella, low fat and light ricotta, lite line, nonfat parmesan, soy/rice cheese (cheddar, mozzarella)
   12. none or fat free cheeses (cheddar, jack, ricotta, cream cheese, healthy choice, alpine lace, etc), soy(tofurella)

10. Circle the type and number of “visible” eggs you eat (scrambled, fried, etc).
   1. six or more whole eggs a week
   2. three to five whole eggs a week
   3. one to two whole eggs a week
   4. one whole egg a month
   5. none or egg whites, egg substitute (nulaid, egg beaters, scramblers, second nature, etc.)
11. Circle the type of eggs usually used in food prepared at home or bought in a grocery stores.
   1. whole eggs or mixes containing whole eggs (complete pancake mix, slice and bake cookies, etc)
   3. combination of egg whites, egg substitute and whole eggs
   5. none or egg whites, egg substitute

   **Fats and Oils**
   Consider your eating habits during the last month.
   For each question, circle all numbers that apply

12. Which kinds of fats are used most often to cook your food (vegetables, meats, etc)?
   1. butter, shortening (with animal fat), lard, bacon grease, chicken fat
   2. shortening (with vegetable fat), vegetable oil (cottonseed)
   3. tub or stick margarine (all except those made from canola oil), vegetable oil (soybean, olive)
   4. vegetable oil (sunflower, corn), tub or stick margarine (made from canola oil)
   5. vegetable oil (canola, safflower)
   6. non or use nonstick cooking spray

   Margarine brand(s) used most often: 1) ___________________ 2) ___________________

13. How much of these “added” fats do you eat in a typical day: peanut butter, margarine, mayonnaise, or salad dressing (including those made with olive oil)? Do not count fat free products.

   **Examples of amounts people often use (None: 3 tsp = 1 Tbsp)**
   1. ten teaspoons or more on toast: 2 tsp margarine
   2. eight to 9 teaspoons on salads: 12 tsp (=¼ cup) salad dressing
   3. six to 7 teaspoons on sandwiches: 6 tsp mayonnaise, 2 tsp margarine
   4. four to 5 teaspoons on potatoes: 3 tsp margarine
   5. three teaspoons on vegetables: 3 tsp margarine
   6. none on pasta, rice: 3 tsp margarine or oil or 6 tsp pesto

14. How often do you eat potato chips, corn or tortilla chips, fried chicken, fish sticks, French fries, doughnuts, croissants or Danish pastries, or other foods?  *Do not count fat free products.*

   1. two or more times a day
   2. once a day
   3. two to 4 times a week
   4. once a week
   5. less than twice a month
   6. never

15. Which best describes the amount of margarine, butter, peanut butter, mayonnaise or cream cheese that you put on bread, muffins, bagels, etc?  *Do not count fat free products*

   1. average
   2. lightly spread (can see the bread through it)
   4. “scrape” (can barely see the spread)
   5. none
16. Which kind of salad dressings do you use?
   1. real mayonnaise
   2. miracle whip, light mayonnaise (5 gm fat per Tbs), Caesar dressing, thousand island dressing
   3. ranch, French, blue cheese or Roquefort, vinegar and oil, Italian, Russian, low fat mayonnaise
dressing, miracle whip light dressing and Italian dressings
   4. Ranch dressing (mix and light mayo)
   5. low cal salad dressing, ranch dressing (mix and low fat yogurt), low fat mayonnaise (1 gm fat per
      Tbs)
   6. Use no salad dressing or fat free mayonnaise, miracle whip fat free, fat free salad dressings, ranch
dressing (mix and nonfat dairy or yogurt/sour cream, vinegar, lemon juice

Sweets and Snacks
Consider your eating habits during the last month.
For each question, circle all numbers that apply

17. How often do you eat desserts or baked goods (sweet rolls, doughnuts, muffins, scones,
cookies, cakes)?
   1. once a day
   2. five to 6 times a week
   3. three to 4 times a week
   4. two times a week
   5. one time a week or less
   6. never

18. Which of the following desserts or snacks have you eaten in the last month?
   1. croissants, cheesecake, typical cakes with frosting
   2. pies, cookies, cupcakes, muffins, scones, frosted doughnuts
   3. granola bars (nature valley, quaker chewy)
   4. low fat muffins, desserts made using lowfat recipes, lowfat cookies (fig bars, ginger snaps,
      snackwell’s) low fat granola bars (power bar, quaker chewy)
   5. fat free desserts including angel food cake, fat free cookies
   6. never eat baked goods listed above or eat fruit for dessert

19. Which of the following snacks have you eaten in the last month?
   1. chocolate, commercial (movie) popcorn, poppy cock popcorn, caramel corn
   2. nuts, potato chips, corn chips, Doritos chips, microwave popcorn, homemade popcorn with butter,
cracker jack, French fries, peanut butter, party/snack crackers (ritz)
   3. tortilla chips, baked potato chips, pretzels, light microwave popcorn, lightly buttered popcorn
      (1tsp margarine for 3 cups popcorn), low fat crackers (soda, graham)
   4. baked tortilla chips, homemade popcorn with no fat, fat free soda crackers and other fat free
      crackers
   5. do not eat snacks or eat fruits and vegetables as snacks

Grains, Beans, Fruits and Vegetables
Consider your eating habits during the last month. For this part of the survey, note that the time frame
varies for the foods listed; some questions ask you to think about how much per day, others per week.

20. How many pieces of fruit or cups of fruit juice do you consume a day (do not include
“fruit flavored” drinks) __________ cups or pieces
21. How many cups of vegetables do you eat a day (tossed salad, cooked vegetables, soups, casseroles, etc)? (A typical serving size for tossed salad is 1 to 1 ½ cups) __________ cups

22. How many cups of legumes do you eat a week (refried beans, split peas, white beans, black beans, black-eyed peas, lentils, chili, etc)? __________ cups

23. How much of the following do you eat a week? (A typical cereal bowl holds 1 to 2 cups; people typically eat 9 to 12 cups of popcorn, which is about what is in one full bag of microwave popcorn)

<table>
<thead>
<tr>
<th>Amounts eaten per week</th>
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</thead>
<tbody>
<tr>
<td>Cooked cereal</td>
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<tr>
<td>Ready to eat cereal</td>
</tr>
<tr>
<td>English muffin</td>
</tr>
<tr>
<td>Hamburger bun</td>
</tr>
<tr>
<td>Bagel (plain or flavored)</td>
</tr>
<tr>
<td>Pita or pocket bread</td>
</tr>
<tr>
<td>Eight inch tortilla</td>
</tr>
<tr>
<td>Plain popcorn</td>
</tr>
<tr>
<td>Fat free or lowfat muffin</td>
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<tr>
<td>Cornbread</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amounts eaten per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread or toast</td>
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<tr>
<td>Dinner or hard roll</td>
</tr>
<tr>
<td>French/sourdough bread</td>
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<tr>
<td>Four inch pancake</td>
</tr>
<tr>
<td>Lowfat crackers such as soda, graham</td>
</tr>
<tr>
<td>Regular sized rice cakes</td>
</tr>
<tr>
<td>Mini sized rice cakes</td>
</tr>
<tr>
<td>Pretzels (1 cup or 1 large soft)</td>
</tr>
</tbody>
</table>

24. How much of the following do you eat a week? Be sure to count these foods when they are in a mixed dish (casserole, pierogies, burrito, etc). This includes breakfast, lunch, and dinner.

<table>
<thead>
<tr>
<th>Number of servings eaten per week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macaroni, spaghetti and other pastas (½ cup/serving)</td>
</tr>
<tr>
<td>Mashed potato (½ cup/serving)</td>
</tr>
<tr>
<td>Baked potato (1 medium/serving)</td>
</tr>
<tr>
<td>Cooked rice, corn, bulger, barley, other grains (½ cup/serving)</td>
</tr>
</tbody>
</table>
Beverages
Consider your eating habits during the last month.
For each question, circle all numbers that apply

25. Which of the following reflects your habits regarding alcohol beverages?

1 drink = 12 ounce beer
1 ½ ounces whiskey, gin, rum, etc.
4 ounces of wine
1 ounce liquor

1. one or more drinks a day
2. four to 6 drinks a week
3. three drinks a week
4. one to 2 drinks a week
5. one to 3 drinks a month
6. do not drink alcohol beverages

26. Which of the following reflects your habits regarding soda pop, sweetened seltzers, sports drinks, fruit punch, etc? Do not count sugar free (diet drinks)

1 can = 12 ounces
big gulp = 32 ounces
1 liter = 33 ounces
2 liters = 67 ounces

1. more than 48 ounces
2. 33-48 ounces
3. 25-32 ounces
4. 12-24 ounces
5. none or less than 12 ounces a week

27. How much coffee do you drink? This includes expressos, lattes, mochas, etc.

Guidelines for Espresso Drinks
“short” = 8 – 10 ounces
small “tall” = 12 ounces
medium “grande” = 16 ounces
large “venti” = 20 ounces

1. more than 40 ounces (more than 5 cups) a day
2. 25-40 ounces (4 to 5 cups) a day
3. 6 – 24 ounces (1 to 3 cups) a day
4. none or less than 1 cup a day
Salt
Consider your eating habits during the last month.
For each question, circle all numbers that apply

28. Which type of salt do you normally use?
   1. regular salt, sea salt, flavoring salts (seasoned, garlic, onion, celery salt, lemon pepper etc), regular soy sauce
   3. combination of regular and lite salt
   4. lite salt, lower sodium soy sauce, reduced sodium flavoring salts
   5. none or salt substitute (100% potassium chloride), salt free products (Mrs. Dash, etc)

29. How often do you add salt to your food at the table?
   1. always
   2. frequently
   4. occasionally
   5. never

30. Which type of salt and how much do you use in cooking potatoes, rice, pasta, vegetables, meat, casseroles, hot cereals, and soups
    1. regular salt (typical amount) or eat in restaurants 4 or more times a week
    2. regular salt (½ typical amount) or lite salt (typical amount)
    4. lite salt (½ typical amount)
    5. none or salt free products (Mrs. Dash, etc) salt substitute

31. Which type of cereals do you use?
    1. typical dry cereals (sweetened or unsweetened) or cereals cooked with regular salt (typical amount)
    3. combination of typical dry cereals and salt-free dry cereals (shredded wheat, puffed wheat, puffed rice) or cereals cooked with regular salt (½ typical amount) or lite salt (typical amount)
    5. do not eat cereal or eat salt-free dry cereals (shredded wheat, puffed wheat, puffed rice, etc) or cereals cooked without salt.

32. How often do you use typical canned, bottled, or packaged foods such as:
    salsa     salad dressing     boxed noodle entrees
    Picante sauce     soups (chicken broth)     frozen entrees
    BBQ sauce     chili     canned beans
    ketchup     cured meats (lunch meat)     canned vegetables
    1. more than 15 times a week or eat in restaurants 4 or more times a week
    2. ten to 14 times a week
    3. six to 9 times a week
    5. five times a week or less

Restaurants and Recipes
Consider your eating habits during the last month.
For each question, circle all numbers that apply

33. How often do you eat breakfast at a restaurant or cafeteria (this includes coffee shops)?
    1. more than twice a week
    2. once or twice a week
    3. once a week and you eat low fat (unbuttered toast or English muffin, oatmeal)
    4. less than once a month
    5. never
Where do you eat breakfast out most frequently?
1) ___________________   2) _____________________

34. How often do you eat lunch at a restaurant or cafeteria or eat “take out”? 
1. daily
2. five days a week
3. two to 4 days a week
4. once a week
5. less than once a month
6. never

Where do you eat lunch out most frequently?
1) ___________________   2) _____________________

35. How often do you eat dinner at a restaurant or cafeteria or eat “take out”? 
1. more than 3 times a week
2. two to 3 times a week
3. once a week
4. once or twice a month
5. less than once a month
6. never

Where do you eat dinner out most frequently?
1) ___________________   2) _____________________

36. Check the choices you make when eating in restaurants or cafeterias (you may check more than one)
- Select restaurants that offer low-fat choices and order these choices
- Order toast, muffins, cereal, pancakes, waffles for breakfast
- Order soup (not cream), salad or other meatless, cheeseless entrees for lunch
- Order vegetarian pizzas with half the cheese
- Avoid cheese, eggs, bacon on salads and avoid potato and macaroni salads
- Put garbanzo or kidney beans on salad at the salad bar
- Use a very small amount of salad dressing
- Order a fish, shellfish, chicken, or lean red meat entrée (but not fried)
- Use no more than 1 pat of margarine at any meal
- Order fruit, sorbet, sherbert, frozen yogurt or skip dessert

37. How often do you eat foods made using low fat recipes or cook low fat without recipes?
1. once a month or less
2. one to 2 times a week
3. three to 4 times a week
4. five to 6 times a week
5. everyday
Seafood
Consider your eating habits during the last month.
For each question, circle all numbers that apply

38. How often do you eat fish? (tuna, snapper, perch, sole, halibut, cod, salmon, shrimp/prawns, crab, lobster, scallops, clams, oysters, sardines, etc)
   1. do not eat fish or eat fish less than once a month
   2. one to 3 times a month
   3. once a week
   4. two times a week
   5. three or more times a week or eat vegetarian with no added fat

39. Which fish (fresh, frozen, or canned) have you eaten in the last month?
   1. ate no fish in the last month
   2. clams, scallops, lobster, crab, perch, cod, sole, snowcrab (surimi)
   3. tuna, halibut, snapper, catfish, shrimp (prawns), squid
   4. salmon (pink, silver, coho, red), trout, steelhead, oysters
   5. salmon (Chinook or king), sardines, herring, mackerel, or eat vegetables with no added fat

Where do you most often buy your fish and seafood?
1) ________________________________ 2) ________________________________
Fiber
Consider your eating habits during the last month.
For each question, circle only one number

**Please note change in instructions above**

<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
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</thead>
<tbody>
<tr>
<td>40. How often do you eat Rice Krispies, Special K, Grapenuts, and/or Corn Flakes?</td>
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<td>1. Never</td>
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<td>2. Once a week or less</td>
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<td>3. 1-2 times a week</td>
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<td>5. 5-6 times a week</td>
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<td>6. Once a day or more</td>
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<tr>
<td>41. How often do you eat Wheaties, Shredded Wheat, All Bran, and/or Raisin Bran?</td>
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<td>1. Never</td>
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<td>2. Once a week or less</td>
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<td>6. Once a day or more</td>
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<td>42. How often do you eat Cheerios, Oatmeal, and/or Quaker Oat Flakes?</td>
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<td>1. Never</td>
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<td>6. Once a day or more</td>
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<td>43. How often do you eat Oat Bran (cooked)</td>
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<td>1. Never</td>
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<td>6. Once a day or more</td>
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<td>44. How often do you eat All Bran’s “Bran Buds”?</td>
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<td>1. Never</td>
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<td>6. Once a day or more</td>
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<td>45. How often do you eat English muffins, white bread, white pita, cornbread, and/or whole wheat bread?</td>
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<td>1. Never</td>
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<td>6. Once a day or more</td>
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<td>46. How often do you eat Rye and/or Pumpernickel bread?</td>
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<td>1. Never</td>
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<td>2. Once a week or less</td>
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<td>5. 5-6 times a week</td>
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<td>6. Once a day or more</td>
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<tr>
<td>47. How often do you eat melon, banana, blueberries, grapes, nectarines, and/or pineapple?</td>
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<td>1. Never</td>
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<tr>
<td>6. Once a day or more</td>
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</tbody>
</table>
48. How often do you eat prunes, fresh or canned peaches, kiwi, apples, mango, and/or canned pears?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more

49. How often do you eat dried apricot, fresh grapefruit, plums, and/or strawberries?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more

50. How often do you eat fresh apricot, orange, and/or fresh pears?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more

51. How often do you eat cauliflower, bean sprouts, corn, cucumber, and/or V-8 juice?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more

52. How often do you eat cabbage, celery, kale, turnips, spinach, canned tomato, zucchini, and/or snow peas?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more

53. How often do you eat asparagus, carrots, green beans, okra, peas, broccoli, and/or sweet potatoes?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more

54. How often do you eat Brussel’s sprouts?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more

55. How often do you eat lentils and/or black-eyed peas?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more

56. How often do you eat chick peas (garbanzos), white (Great Northern), lima, and/or butter beans?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more

57. How often do you eat broad beans, black, navy, and/or kidney beans?
1 Never  
2 Once a week or less  
3 1-2 times a week  
4 3-4 times a week  
5 5-6 times a week  
6 Once a day or more
BIBLIOGRAPHY


