AN ABSTRACT OF THE THESIS OF

Jennifer N. Slawta for the degree of Doctor of Philosophy in Human Performance presented on March 3, 2000. Title: Physical Activity and Coronary Heart Disease Risk in Women with Multiple Sclerosis.

Abstract Approved: Redacted for Privacy

Anthony R. Wilcox

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The aim of the first manuscript was to examine CHD risk in women with MS by assessing the frequency of physical inactivity and the frequency of anthropometric, dietary, and metabolic CHD risk factors. Although participation in physical activity is often avoided by many women with MS, some women remain physically active despite their disability. The aim of the second manuscript was to determine whether active women with MS were at lower CHD risk than inactive women with MS by assessing the differences in abdominal fat accumulation and levels of triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), and glucose.

The study sample consisted of 123 women with MS, aged 23 to 72 years (49.9±10 years). Venous blood was collected for measurement of lipids, lipoprotein-cholesterol, and glucose. Skinfold thicknesses and girth circumferences were obtained for estimation of total and abdominal body fat. Leisure-time physical activity (LTPA) during the previous week was assessed with a modified version of the Yale Physical Activity Survey. LTPA during the last 12 months was assessed with the physical activity questionnaire used in the Postmenopausal Estrogens/Progestins Intervention Trial. Eating habits were assessed by the Block Food Frequency Questionnaire.

In the total sample, 27.3% had low HDL-C, 19.8% had high TG, 8.3% had high glucose, 68.3% reported regular participation in LTPA, 52% were abdominally obese, and 69% exceeded recommendations for dietary fat intake. LTPA was significantly

associated with lower waist circumferences ($p=0.0001$), lower TG levels ($p=0.0005$), lower glucose levels ($p=0.002$), and marginally with higher HDL-C levels ($p=0.09$). After adjusting for the covariates known to influence the CHD risk factors, women reporting participation in low- to moderate-intensity LTPA had significantly lower waist circumferences, TG levels, and glucose levels relative to inactive women.

CHD risk in this sample of women with MS was comparable to the CHD risk in the general population of women without MS with respect to anthropometric, dietary, and metabolic CHD risk factors. Women with MS reporting participation in any intensity of LTPA, however, were at significantly lower CHD risk relative to women with MS reporting no participation in LTPA.

Physical Activity and Coronary Heart Disease Risk in Women with Multiple Sclerosis

by

Jennifer N. Slawta

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I understand that my thesis will become part of the permanent collection of the Oregon State University libraries. My signature below authorizes release of my thesis to any reader upon request.

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Dr. Jeffrey McCubbin and Dr. Anthony Wilcox were involved in the design and analysis of each manuscript. Darek Nalle assisted with the analysis and interpretation of the data.

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PHYSICAL ACTIVITY AND CORONARY HEART DISEASE RISK IN WOMEN WITH MULTIPLE SCLEROSIS

INTRODUCTION: BACKGROUND AND SIGNIFICANCE

Multiple Sclerosis (MS) is an autoimmune disease by which the body's immune system mistakenly attacks the myelin sheaths surrounding nerve fibers in the central nervous system (87,103). Damage to the myelin sheaths disrupts smooth muscle conduction of electrical impulses in the central nervous system causing a number of sensory and motor impairments (87,89,103). There are currently between 250,000 and 400,000 physician-diagnosed cases of MS in the United States (3,103), and 8,000 new cases are diagnosed each year (87). With the continual development of new medications for the treatment of MS, persons with MS are living longer, which in turn, increases their risk for developing age-related secondary chronic conditions including coronary heart disease (CHD) (89,105,113). The greatest proportion of medical costs in the United States, estimated to be between 50 billion and 100 billion dollars annually, is directed toward the treatment of CHD (36). Therefore, in addition to the health care burden placed on the treatment of MS, an additional health care burden exists from age-related secondary medical problems that may arise in persons with MS.

MS affects twice as many women than men (87,113) and CHD is responsible for the majority of deaths in women in the United States (36). In this regard, the United States Surgeon General emphasizes the need for research focusing on preventive measures for reducing CHD risk, specifically in women and those with disabilities (123). The prevalence of CHD in women can be largely reduced by effective population-based strategies aimed at lifestyle and behavior modification, including greater participation in physical activity and reductions in dietary intake of total and saturated fat. Physical inactivity and high dietary intake of total and saturated fat are known risk factors for CHD (36,109). Physical inactivity is linked with greater amounts of total and abdominal fat, higher circulating levels of triglycerides (TG), lower circulating levels of high-density lipoprotein-cholesterol (HDL-C), and reduced insulin sensitivity, which is represented by high circulating levels of insulin and glucose

(21,31,36,123). In fact, physically inactive individuals have a twofold increased risk for CHD mortality relative to their physically active counterparts (82). High dietary intake of total fat, specifically saturated fat, is linked with higher levels of total cholesterol and low-density lipoprotein-cholesterol (LDL-C) (36), and is weakly linked with the onset and/or progression of MS (117). Among women, high TG levels and low HDL-C levels are stronger predictors for CHD than high levels of total cholesterol and LDL-C (72). In this regard, data from the Lipids Research Clinics' Follow-up Study indicate an almost threefold increase in cardiovascular disease death among women with low circulating levels of HDL-C ($\leq$ 50 mg/dL) relative to women with high circulating levels of HDL-C (>50 mg/dL). Furthermore, in the presence of low HDL-C levels, high TG levels ($\geq$200mg/dL) are associated with an eightfold increase in cardiovascular disease death in women (72). Physical activity improves circulating levels of TG and HDL-C by stimulating lipoprotein lipase, a key enzyme responsible for the degradation of TG and formation of HDL-C, and inhibiting hepatic lipase and cholesterol ester transfer protein, key enzymes responsible for the degradation of HDL-C (21,59,82,126).

Insulin resistance, manifested by a loss of sensitivity of the body's tissues to insulin, causes circulating levels of glucose to rise and is responsible for the onset of noninsulin dependent diabetes mellitus (NIDDM) (96,98). Insulin resistance is believed to be largely responsible for CHD-related metabolic disorders including high levels of TG and low levels of HDL-C (21,24,57). In fact, the risk for cardiovascular disease is three times higher in diabetic women relative to their nondiabetic counterparts (55). Physical activity reduces CHD risk by improving the sensitivity of receptors on target tissues to insulin, which in turn stimulates the target tissues to remove glucose from the circulation (21,124).

Increasing amounts of total body and abdominal fat are associated with, and may precede, increases in circulating levels of TG (13,21,24,25,88,91,92), decreases in circulating levels of HDL-C (13,17,21,24,25,88,91,92), and insulin resistance (21,24,57,88). Abdominal fat accumulation is believed to be an even more important determinant of disease risk than total body adiposity (21,24,57). More specifically, increases in lipolytic activity of abdominal fat cells contribute to high levels of plasma free fatty acids, which may be the initial metabolic disorder responsible for insulin

resistance and unfavorable levels of TG and HDL-C (21,24). Recent evidence suggests that the waist circumference may be the most accurate anthropometric measure of abdominal and visceral (intra-abdominal) obesity in women (91). Waist circumferences greater than 80 cm are associated with increased health risks, and waist circumferences greater than 96.5 cm are associated with a threefold increased risk for a CHD-related event (101). Physical activity is believed to attenuate the age-related increases in total and abdominal obesity and their associated metabolic and hormonal disturbances (21).

Because the symptoms of MS can profoundly interfere with and limit participation in life activities and health promotion practices (113,114,115), in particular, physical activity, by women with MS, they may be at additional risk for CHD as they age. Limited research suggests that women with MS are less active than age-matched women without MS (76,87). In fact, just the diagnosis of MS, independent from the clinical status and severity of MS, is believed to be responsible for the low physical activity levels in women with MS (76). Thus, *the aim of the first manuscript was to examine CHD risk in a sample of women with MS by assessing the frequency of physical inactivity and the frequency of anthropometric, dietary, and metabolic CHD risk factors.* The aim of the first manuscript was intended to determine whether women with MS were at greater risk for CHD than the general population of women without MS by comparing physical activity practices, body composition, dietary habits, and metabolic measurements in the present sample of women with MS to the general population of women screened from large population surveys including the Behavioral Risk Factor Surveillance System (BRFSS) (93,123), the National Health Interview Survey (NHIS) (123), the third National Health and Nutritional Examination Survey (NHANES III) (38), and the Lipids Research Clinics' Follow-up Study (72).

The National Cholesterol Education Program (36), the American Heart Association (39), and the United States Surgeon General (123) strongly recommend physical activity as a principal component of primary CHD–risk factor management aimed at lowering abdominal fat accumulation, lowering levels of TG, raising levels of HDL-C, and improving insulin sensitivity. Although participation in physical activity is avoided by many women with MS (76,114), some women remain physically active despite their disability. At present, it is unknown whether women with MS are able to

participate in enough physical activity to achieve health-related benefits and to reduce their risk for CHD. Thus, *the aim of the second manuscript was to assess the differences in abdominal fat accumulation and levels of TG, glucose, and HDL-C between women with MS reporting greater participation in higher intensity physical activity and inactive women with MS.* The aim of the second manuscript was intended to determine what intensity of physical activity might be necessary to reduce CHD risk in women with MS.

It is undetermined whether physical activity-related improvements in the metabolic CHD risk factors are independent from physical activity–related reductions in total body and abdominal fat. Evidence from several studies suggests that favorable levels of the metabolic CHD risk factors observed in physically active individuals are mediated through lower levels of total body and abdominal fat also observed in physically active individuals (31,48,128,131). For example, Duncan et al. (29) identified women with the greatest reduction in body fat to have the greatest rise in HDL-C levels when combining women from all intensity-intervention groups following six months of exercise training.

By contrast, some evidence has demonstrated that favorable improvements in the metabolic CHD risk factors with physical activity can occur in the absence of fat loss and are primarily mediated by a physical activity–related increase in lipoprotein lipase activity (4,19,50,56,59,104,112,120,126). In this regard, reductions in TG (19) and glucose (50) levels and elevations in HDL-C levels (4,19,56,104) are observed immediately following, or in the first few days that follow an acute exercise bout, independent from a change in body composition. If exercise is not repeated, a considerable amount of the favorable changes in TG, glucose, and HDL-C are lost within 48 to 72 hours following the last exercise bout (19,50,56), which supports the hypothesis that CHD risk–reducing changes in the metabolic CHD risk factors are achieved by repeated bouts of acute exercise, whereas reductions in total body and abdominal fat may be more related to chronic exercise training. In turn, chronic exercise–related reductions in body fat may have long-term additive effects on improving the metabolic CHD risk factors achieved by repeated bouts of acute exercise. Therefore, *the second manuscript addressed whether the association between physical*

activity and the metabolic CHD risk factors was independent from levels of total body and abdominal fat in the sample of women with MS, and whether total body fat or abdominal fat acted as a stronger biological modulator in the causal pathway between physical activity and the metabolic CHD risk factors.

Current physical activity recommendations endorsed by the United States Surgeon General (123) and the Centers for Disease Control and Prevention (82) emphasize at least 30 minutes of moderate-intensity physical activity on most days of the week. The current physical activity recommendations are based on research which suggests that frequent bouts of low- to moderate-intensity physical activity can lower CHD risk similar to a single, longer bout of high-intensity physical activity (2,29,30,54,73,123). For instance, comparable improvements in body composition (2,30,45,54) and some metabolic CHD risk factors (2,30) are observed between those incorporating intermittent bouts of moderate-intensity physical activity into their daily schedules and those participating in a single, more structured bout of physical activity at least three times each week. When controlling for energy expenditure, comparable rises in levels of HDL-C are observed between low- and high-intensity female walkers (29), and comparable reductions in noninsulin dependent diabetes mellitus risk are observed between vigorously and moderately active women (51). Less abdominal fat accumulation and lower levels of glucose are observed in older adults (85) and viscerally obese older adults (84) reporting participation in low-intensity physical activity related to daily living relative to older adults and viscerally obese older adults reporting little or no participation in light-intensity physical activity related to daily living. King et al. (60) report that increases in HDL-C greater than 5 mg/dL were achieved by more than 50% of low- to moderate-intensity older adult exercisers, whereas only 30 to 35% of high-intensity older adult exercisers achieved increases in HDL-C levels greater than 5 mg/dL following two years of exercise intervention. The greatest magnitude of reduction in CHD mortality is observed in previously inactive individuals who become lightly to moderately active (47). Therefore, the current physical activity recommendations are intended for those who are the most inactive because they have the most to gain from a public health standpoint (47).

By encouraging frequency and diversity of physical activity, and reducing the emphasis on the intensity of physical activity, the current physical activity guidelines may be attainable for many women with MS. Although limited evidence suggests that persons with MS are capable of participating in (86,87,89,108) and achieving health-related benefits (86,87,108) associated with moderate-intensity physical activity, several perceived barriers, including fatigue, mobility, transportation, and fear limit the extent by which many persons with MS can effectively incorporate physical activity into their daily lives (113,114,115). Therefore, it is essential that strategies be developed specifically for persons with MS to overcome potential barriers prohibiting participation in physical activity practices. Furthermore, the lack of sufficient data regarding appropriate exercise prescription guidelines necessary to reduce CHD risk and other secondary chronic conditions in women with MS is a major obstacle to convincing health care professionals to include exercise prescription into their existing treatment of patients with MS. Thus, *an important objective of the second manuscript was to provide valuable information which would be helpful in establishing minimal physical activity recommendations necessary to reduce CHD risk in women with MS.*

HEALTH BEHAVIORS AND CORONARY HEART DISEASE RISK IN WOMEN WITH MULTIPLE SCLEROSIS

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ABSTRACT

Background: The United States Surgeon General emphasizes the need for research addressing coronary heart disease (CHD) risk in women and those with disabilities. Health behavior habits, including physical activity and dietary habits, can influence the risk for CHD by their association with total body and abdominal fat accumulation, insulin sensitivity, and levels of lipids and lipoproteins. Because health promotion practices frequently decline with increasing disability, women with multiple sclerosis (MS) may be at additional risk for CHD as they age. Thus, the primary aim of the study was to assess the frequency of physical inactivity and the frequency of anthropometric, dietary, and metabolic CHD risk factors in a sample of women with MS.

Methods: The study sample consisted of 123 women with MS, aged 23 to 72 years. Venous blood was collected for measurement of lipids, lipoprotein-cholesterol, and glucose. Skinfold thicknesses and waist circumferences were obtained for estimation of total body and abdominal fat. Leisure-time physical activity (LTPA) during the previous week was assessed by a modified version of the Yale Physical Activity Survey. Eating habits were assessed by the Block Food Frequency Questionnaire. A brief medical history questionnaire was administered to obtain information regarding medication use, cigarette and alcohol use, and mobility levels.

Results: In the total sample, 44.6% had high total cholesterol, 22.3% had high low-density lipoprotein-cholesterol (LDL-C), 21.5% had high triglycerides (TG), 8.3% had high glucose, and 27.3% had low high-density lipoprotein-cholesterol (HDL-C). Almost 50% of the participants were overweight, 25% of participants were obese, and 52% of participants were abdominally obese. Approximately 69% of the participants exceeded recommendations for dietary intakes of total fat, and 36% exceeded recommendations for saturated fat. The majority of women reported regular participation in some intensity of LTPA (68.3%). Pre- and postmenopausal women using hormones had more favorable levels of some metabolic CHD risk factors relative to pre- and postmenopausal women not using hormones.

Conclusions: The majority of subjects reported participation in light- to moderate-intensity LTPA. Still, CHD risk in this sample of women with MS was comparable to

the CHD risk in the general population of women with respect to anthropometric, dietary, and metabolic CHD risk factors. Because CHD is the leading cause of death in women in the United States, these results emphasize the need for effective, attainable, and attractive strategies for reducing CHD risk in women with and without MS.

INTRODUCTION

The majority of women with MS will live at least 90% of a full life span (103), which increases their risk for developing age-related diseases including CHD (89,105,113). In fact, CHD is responsible for the majority of deaths in women in the United States (36). The prevalence of CHD in women can be largely reduced by effective population-based strategies aimed at lifestyle and behavior modification, including greater participation in physical activity and reductions in dietary intake of total and saturated fat. The symptoms of MS, however, can limit the extent by which many women with MS can effectively and consistently incorporate health promotion practices into their daily lives (113,114,115). Therefore, women with MS may be at additional risk for developing CHD as they age.

Physical inactivity and high dietary intake of total and saturated fat are known risk factors for CHD (36,109). Physical inactivity is linked with greater amounts of total body and abdominal fat, higher circulating levels of TG, lower circulating levels of HDL-C, and reduced insulin sensitivity, which is represented by high circulating levels of insulin and glucose (21,31,36,123). In fact, physically inactive individuals have a twofold increased risk for CHD mortality relative to their physically active counterparts (82). High dietary intake of total fat and saturated fat are linked with higher levels of total cholesterol and LDL-C (36), and greater amounts of body fat (43). Among women, high TG levels and low HDL-C levels are stronger predictors for CHD than high levels of total cholesterol and LDL-C (72). In this regard, data from the Lipids Research Clinics' Follow-up Study indicate an almost threefold increase in cardiovascular disease death among women with low circulating levels of HDL-C ($\leq$ 50 mg/dL) relative to women with high circulating levels of HDL-C (>50 mg/dL) (72). In the presence of low HDL-C levels, high TG levels ($\geq$ 200 mg/dL) are associated with an eightfold increase in cardiovascular disease death in women (72).

Insulin resistance, manifested by a loss of sensitivity of the body's tissues to insulin, causes circulating levels of glucose to rise (96,98) and is associated with high TG and low HDL-C levels (21,24,57). Furthermore, increasing amounts of abdominal fat are associated with, and are believed to precede, increases in levels of TG

(13,21,24,25,88,91,92) and glucose (21,24,57,88), and decreases in levels of HDL-C (13,17,21,24,25,88,91,92).

Current physical activity recommendations, endorsed by the United States Surgeon General (123), the Centers for Disease Control and Prevention (82), and the American Heart Association (109), emphasize at least 30 minutes of moderate-intensity physical activity on most days of the week. The National Cholesterol Education Program (36) and the American Heart Association (109) recommend that dietary intake of total fat be 30% or less of total caloric intake, and dietary intake of saturated fat be 10% or less of total caloric intake. Recommendations for anthropometric indices of body composition for women include body mass index (BMI) to be less than 25 kg/m^2 (43,135), waist circumference to be less than 80 cm (135), and total adiposity to be less than 35% (70). Recommendations for fasting levels of lipids, lipoproteins, and glucose for women are as follows (36,72): total cholesterol < 200 mg/dL; LDL-C < 130 mg/dL; TG < 200 mg/dL; HDL-C > 50 mg/dL; and glucose < 110 mg/dL.

The primary aim of the study was to examine CHD risk in women with MS by assessing the frequency of inactivity and the frequency of anthropometric, dietary, and metabolic CHD risk factors in a sample of women with MS. The primary aim was intended to determine whether women with MS were at greater risk for CHD than the general population of women without MS by comparing physical activity practices, body composition, dietary habits, and metabolic measurements in the present sample of women with MS to the general population of women screened from large population surveys including the Behavioral Risk Factor Surveillance System (BRFSS) (93,123), the National Health Interview Survey (NHIS) (123), the third National Health and Nutritional Examination Survey (NHANES III) (38), and the Lipids Research Clinics' Follow-up Study (72).

In addition, because hormone use is known to influence the metabolic CHD risk factors (15,52,136), *the frequency of high levels of total cholesterol, LDL-C, TG, and glucose, and low levels of HDL-C were examined in postmenopausal women using hormone replacement therapy (HRT) and postmenopausal women not using HRT, and*

in premenopausal women using oral contraceptives and premenopausal women not using oral contraceptives, in order to determine whether hormone users with MS were at lower CHD risk than nonhormone users with MS.

METHODS

The present study was a descriptive study examining the health behaviors, body composition, and lipid, lipoprotein-cholesterol, and glucose levels in women with MS. Women volunteers (n=123) were recruited from Oregon MS chapters, physician referrals, and newspaper announcements. Women with diagnosed cardiovascular disease, insulin-treated diabetes, gout, or recently diagnosed thyroid disorder, and women who currently used oral prednisone, smoked more than ten cigarettes per day, or consumed more than four alcoholic beverages per day were excluded. All subjects had physician-diagnosed MS.

Official approval for the research project was granted by Oregon State University, Corvallis; Rogue Valley Medical Center, Medford; and Oregon Health Sciences University, Portland. The Institutional Review Board proposal is included in appendix A. Data was collected from the MS clinic at Oregon Health Sciences University, the Health and Human Performance Lab at Oregon State University, the Asante Health Promotion offices at Rogue Valley Medical Center, the Springfield Willamalane Senior Activity Center, the Three Rivers Hospital in Grants Pass, and the Salem Hospital Rehabilitation Center. An informed consent was completed by each participant prior to data collection. The informed consent form is included in appendix B.

Assessment of Lipids, Lipoprotein-Cholesterol, and Glucose

Venous blood (< 10 ml) was collected by venipuncture following a 12-hour fast by trained lab technicians using sterile procedures. Firm pressure and a bandage was applied to the venipuncture site immediately following blood collection. Serum and red blood cells were separated by centrifugation at 1900 x g for 15 minutes. The serum was transferred to plastic, labeled vials and frozen at –70° C for later analysis of lipid/lipoprotein-cholesterol (total cholesterol, TG, HDL-C, and LDL-C) and glucose concentrations by Rogue Valley Medical Center.

Quality control of the Rogue Valley Medical Center laboratory is monitored by the Lipid Standardization Program of the Centers for Disease Control and Prevention. Measurements of lipid/lipoprotein-cholesterol and glucose were within specific limits established by the Lipid Standardization Program of the Centers for Disease Control and Prevention (i.e., 2.6 SD, 1.23% CV for total cholesterol; 2.3 SD, 1.41% CV for TG; 1.2 SD, 1.89% CV for HDL-C; and 1.2 SD, 3.26% CV for glucose).

Total cholesterol concentrations were determined by enzymatic procedures in serum with cholesterol esterase, cholesterol oxidase, and peroxidase, which produce colored products that are analyzed with spectrophotometers (125). TG concentrations were determined by enzymatic procedures in serum with glycerol kinase, glycerolphosphate oxidase, and peroxidase. Again, colored products produced are spectrophometrically analyzed (125). HDL-C levels were determined using the direct EZ-HDL Sigma assay, which uses anti human 9-lipoprotein antibody to bind with LDL, VLDL, and chylomicrons. HDL-C levels can then be directly analyzed by enzymatic procedures previously described for total cholesterol. High correlations are reported for HDL-C levels between the Sigma method and standard enzymatic methods used after precipitation of beta lipoproteins with magnesium/dextran sulfate ($r=0.98$). After directly measuring the concentrations of total cholesterol, TG, and HDL-C, LDL-C can be calculated indirectly with the Friedwald equation (40):

$$\text{LDL-C} = \text{Total cholesterol} - \text{HDL-C} - \text{TG}/5$$

Glucose concentrations were determined by an oxygen rate method with a Beckman Oxygen electrode. After adding glucose oxidase to the glucose sample, electronic circuits measure the oxygen consumption rate, which is directly proportional to the glucose concentration in the sample.

Because blood samples were initially going to be analyzed by Dr. Rosemary Wander's Lipid Laboratory at Oregon State University, all samples were collected in plasma EDTA tubes during the first week of testing. There was, however, an unexpected early closure and relocation of Dr. Wander's Lipid Laboratory before all blood samples could be collected. Although the laboratory at Rogue Valley Medical Center agreed to analyze the blood samples for lipid/lipoprotein-cholesterol and glucose concentrations, the laboratory was unable to accurately determine total cholesterol from

samples collected in plasma EDTA tubes, estimating ≤24% bias. The majority of the participants returned the following week to have their blood recollected in serum separator tubes so that their total cholesterol levels could be analyzed by the Rogue Valley Medical Center laboratory. Values for total cholesterol and LDL-C are missing from nine subjects who participated in the study during the first week of data collection but were unable to return for a blood redraw. Because the methods used by the Rogue Valley Medical Center laboratory could accurately determine levels of TG, HDL-C, and glucose obtained in the plasma EDTA tubes, concentrations of TG, HDL-C, and glucose from the nine subjects who did not return for a blood redraw were included in the data analysis. We were unable to obtain blood samples from two subjects. Thus, all measurements of lipid/lipoprotein-cholesterol and glucose are missing from these two subjects. Finally, because the Friedwald equation, which is used to calculate LDL-C from total cholesterol, HDL-C, and TG, is invalid when TG levels exceed 400 mg/dL, LDL-C levels are missing from two subjects who had TG levels greater than 400 mg/dL.

Anthropometry for Assessment of Total and Abdominal Fat

Body weight was measured with a standard balance-beam scale in light clothing without shoes at the Corvallis, Portland, Medford, and Grants Pass testing sites, and with a digital scale at the Springfield and Salem testing sites. For participants who were unable to stand, body weight was obtained on a chair scale when feasible. Three participants were weighed on a chair scale. Weight was not obtained for five nonambulatory participants. An estimate of weight for these five participants was obtained from their physician. Height was measured without shoes using a stadiometer. Participants tested at locations which lacked a stadiometer or who were unable to stand were asked to contact their physician for their height. Measurements (and estimates) of weight and height were used to calculate BMI.

The waist circumference was used as a measure of abdominal fat accumulation. Waist circumference was measured with a tape measure at the narrowest portion of the torso between the top of the iliac crest and the lowest rib. Continuous measurements of

waist circumference were conducted until measurements were within 1 cm agreement. For the participants who were unable to stand, waist circumference was measured in a reclining position when feasible.

Total body fat was calculated from multicomponent prediction equations using skinfold thicknesses as an estimate of subcutaneous fat (127). Skinfold thicknesses were measured with a Lange skinfold caliper at four sites on the right side of the body (triceps, subscapular, abdomen, and calf) according to standardized procedures (49). To reduce standing time for the participants, however, skinfold measurements for the triceps, subscapular, and calf were obtained in a sitting position. Abdominal skinfold measurements were obtained in a standing position. For the participants unable to stand, abdominal skinfold measurements were obtained in a reclining position. Continuous measurements of skinfold thicknesses were conducted in rotational order until measurements for each site were within 1 mm agreement. The sum of the four skinfold sites were used in the following multicomponent prediction equation for women (127).

$$\%BF = 0.428(\text{sum skinfolds}) - 0.0011(\text{sum of skinfolds}^2) + 0.127(\text{age}) - 3.01$$

The multicomponent prediction equations used in the present study were chosen because 1.) they were developed on women between the ages of 34 and 84, 2.) they account for individual differences in the mineral and water components of fat free mass, 3.) they yield high multiple correlation coefficients between skinfold thicknesses and body fat (ranging from 0.88 to 0.91) and small standard error estimates (ranging from 2.6 to 3.2), and 4.) they have been used previously in the literature to estimate body fat specifically in women with MS (86).

Physical Activity Assessment

A modified version of the second section of the Yale Physical Activity Survey was used to gain information regarding the frequency and duration of participation in vigorous-intensity LTPA (i.e., activities comparable to fast walking $\geq$ 4.5 mph such as jogging, lap swimming, stairmaster), moderate-intensity LTPA (i.e., activities comparable to brisk walking between 3.0 mph and 4.0 mph, such as water aerobics),

and light-intensity LTPA (i.e., activities comparable to leisurely walking between 2.0 mph and 3.0 mph, such as yoga, tai chi, and stretching). A copy of the modified Yale Physical Activity Survey in included in appendix C.

Diet Composition

Eating habits and diet composition were assessed by the Block Food Frequency Questionnaire (BFFQ). The BFFQ provides valid and reliable information regarding dietary intake of total fat, saturated fat, and nutritional supplements (8). The BFFQ was analyzed by Block Dietary Data Systems. A copy of the BBFQ is included in appendix D.

Medical History

A brief medical history questionnaire was administered to obtain information regarding medication and hormone use, current and past cigarette use, alcohol consumption, and mobility levels. A copy of the medical history questionnaire is included in appendix E.

Statistics

Summary statistics were used to report the 1.) anthropometric characteristics, health behavioral characteristics, metabolic characteristics, and medication use of the participants, and 2.) frequency of anthropometric, dietary, and metabolic risk factors associated with increased health risks among all participants, all postmenopausal participants, all premenopausal participants, and postmenopausal and premenopausal participants stratified on hormone use. Mean differences in the levels of total cholesterol, LDL-C, TG, glucose, and HDL-C between postmenopausal and premenopausal women, postmenopausal women using HRT and postmenopausal

women not using HRT, and premenopausal women using oral contraceptives and premenopausal women not using oral contraceptives were analyzed using independent *t*-tests with an alpha level of 0.05.

RESULTS

Table 1.1 summarizes the anthropometric characteristics, health behavioral characteristics, metabolic characteristics, and medication use of the participants. Mean levels of BMI, waist circumference, and total body fat exceeded levels recommended by the World Health Organization (135). Mean levels of dietary intake of total fat exceeded levels recommended by the National Cholesterol Education Program (109) and the American Heart Association (109), but mean levels of dietary intake of saturated fat were within recommendations. The majority of the participants were current nonsmokers (94.3%), rarely consumed alcohol (69.9%), and used some form of multivitamin or antioxidant supplement (79.7%). Slightly less than half of the participants met the current daily recommendations for dietary intake of vegetables (47.7%) and fruit (47.7%). The frequency of antidepressant use was 38.2%, postmenopausal HRT use was 74.3%, and premenopausal oral contraceptive use was 20.4%. Less than half of the participants were employed (42.3%).

The study sample represented a high functioning, less disabled group of women with MS in that approximately 85.4% were ambulatory, 12.2% regularly used a wheelchair, and only 1.6% had to be in bed most or all of the time (table 1.1). The majority of women reported regular participation in some intensity of LTPA (light, moderate, or vigorous) accumulating 150 minutes during the previous week. Approximately 10.6% of women reported regular participation in vigorous-intensity LTPA, and 31.7% reported either irregular or no participation in LTPA during the previous week (table 1.1).

Table 1.1: Anthropometric Characteristics, Health Behavioral Characteristics, Metabolic Characteristics, and Medication Use of the Participants (n=123)

Age, yr	49.9±10.0
Anthropometric Characteristics (values are means ± SD)	
Body Mass Index (kg/m^2)(n=120)	26.0±6.5
Waist Circumference (cm)(n=122)	82.4±13.8
Body Fat (%)(n=122)	37.1±7.9
Dietary Behaviors	
Total Fat Intake (%) (mean±SD)	33.4±7.9
Saturated Fat Intake (%)(mean±SD)	9.2±3.2
Vitamin/Antioxidant Use (# participants/percent)	98 (79.7)
Vegetable Intake (>3/day) (# participants/percent)	58 (47.1)
Fruit Intake (>2/day) (# participants/percent)	58 (47.1)
Cigarette Use (values are number participants/percent)	
Current (<10/day)	7 (5.7)
Past	42 (34.1)
Never	81 (65.9)
Alcohol Intake (values are number participants/percent)	
>1 drink/week	37 (30.1)
<1 drink/week	16 (13.0)
Never	70 (56.9)
Mobility (values are number participants/percent)	
Ambulatory (with or without aids)	106 (86.0)
Nonambulatory (wheelchair/scooter)	15 (12.2)
Nonambulatory (in bed most/all of the time)	2 (1.6)
Leisure Time Physical Activity (values are number participants/percent)	
Inactive	19 (15.4)
Light/Moderate	80 (65.0)
Vigorous	13 (10.6)
Recommended	84 (68.3)
Metabolic (values are means ± SD)	
Triglyceride (mg/dL)(n=121)	147.9±79.6
HDL-C (mg/dL)(n=121)	60.0±13.6
Glucose (mg/dL)(n=121)	92.2±11.3
Total Cholesterol (mg/dL)(n=112)	197.8±39.6
LDL-C (mg/dL)(n=112)	107.2±33.2
Medication Use (values are number participants/percent)	
Antidepressant (%)	47 (38.2)
Postmenopausal HRT (%)*	55 (74.3)
Premenopausal Oral Contraceptive (%)†	10 (20.4)
Employment (value is number participants/percent)	52 (42.3)

HDL-C, High-density lipoprotein-cholesterol
LDL-C, Low-density lipoprotein-cholesterol
HRT, Hormone Replacement Therapy

*N=74 postmenopausal participants
†N=49 premenopausal participants

Table 1.2 provides data regarding the frequency of participation in specific LTPA reported by women in the present sample and women participating in the NHIS. The most common activities reported by women participating in the present study were gardening (50.4%), leisurely walking (49%), and stretching (25.5%). Walking for exercise (brisk and leisure) was the leading activity reported by women from both samples. The frequency of walking, however, was slightly greater in the present sample (55.3%) relative to women participating in the NHIS (48.3%), yet leisurely walking (49%) was reported with greater frequency than brisk walking (21.9%) in the present sample. Swimming/water activities, strengthening exercises, and gardening were more frequently reported by women participating in this study relative to those participating in the NHIS. By contrast, participation in more vigorous activities (jogging, stair climbing, and aerobics) were reported with less frequency in the present sample relative to women from the NHIS.

Table 1.2: Participation in Common Leisure-Time Physical Activities Reported by the Present Sample of Women with MS and Women Screened in the NHIS, 1991

Activity Category	MS Sample	NHIS
Gardening	50.4%	25.1%
Walking (leisure)	49.0%	
Walking (brisk)	21.9%	
Walking (leisure + brisk)	55.3%	48.3%
Stetching	25.5%	24.4%
All Water Activities	20.3%	15.0%
Weight Lifting/Strengthening Exercises	13.8%	8.8%
Bicycle/Exercycle	12.2%	14.6%
Jogging	2.4%	5.7%
Stair Climbing	2.4%	11.6%
Golf	1.6%	1.8%
Aerobics/Aerobic Dance	0%	11.1%

Table 1.3 summarizes the frequency of anthropometric, dietary, and metabolic risk factors associated with increased CHD risk among participants. In the total sample, 27.3% had low levels of HDL-C (≤50 mg/dL), 21.5% had high levels of TG (≥200 mg/dL), 8.3% had high levels of glucose (≥110 mg/dL), 44.6% had high levels of total cholesterol (≥200 mg/dL), and 22.3% had high levels of LDL-C (≥130 mg/dL). Almost 50% of the participants were overweight (BMI ≥ 25 kg/m^2) and half of these participants were obese (BMI ≥ 30 kg/m^2) as defined by the World Health Organization (135). Approximately 68% of the participants exceeded a total adiposity of 35%, 52% of the participants had waist circumferences exceeding 80 cm, and 16% of the participants had waist circumferences exceeding 96.5 cm. Dietary intake of total fat was greater than 30% of total caloric intake in the majority of the participants (69.1%), and dietary intake of saturated fat was greater than 10% of total caloric intake in almost 36% of the participants.

Table 1.3: Frequency of Participants at Increased CHD Risk from Anthropometric, Dietary, and Metabolic Risk Factors (N=123)

Anthropometric Factors (values are number participants/percent)	
Body Mass Index > 25 kg/m^2†	57 (47.5)
> 30 kg/m^2†	31 (25.8)
Waist Circumference > 80 cm*	63 (52.0)
> 96.5 cm*	19 (16.0)
Body Fat > 35%*	83 (68.0)
Dietary Factors (values are number participants/percent)	
Total Fat Intake > 30%	85 (69.1)
Saturated Fat Intake > 10%	44 (35.8)
Metabolic Factors (values are number participants/percent)	
HDL-C < 50 mg/dL**	33 (27.3)
Triglyceride > 200 mg/dL**	26 (21.5)
Glucose > 110 mg/dL**	10 (8.3)
Total Cholesterol > 200 mg/dL††	50 (44.6)
LDL-C > 130 mg/dL††	25 (22.3)

HDL-C, High-density lipoprotein-cholesterol
LDL-C, Low-density lipoprotein-cholesterol

*N=122 because of missing values
**N=121 because of missing values
†N=120 because of missing values
††N=112 because of missing values

Figure 1.1: Percent of Premenopausal and Postmenopausal Participants at Increased CHD Risk from Metabolic Risk Factors

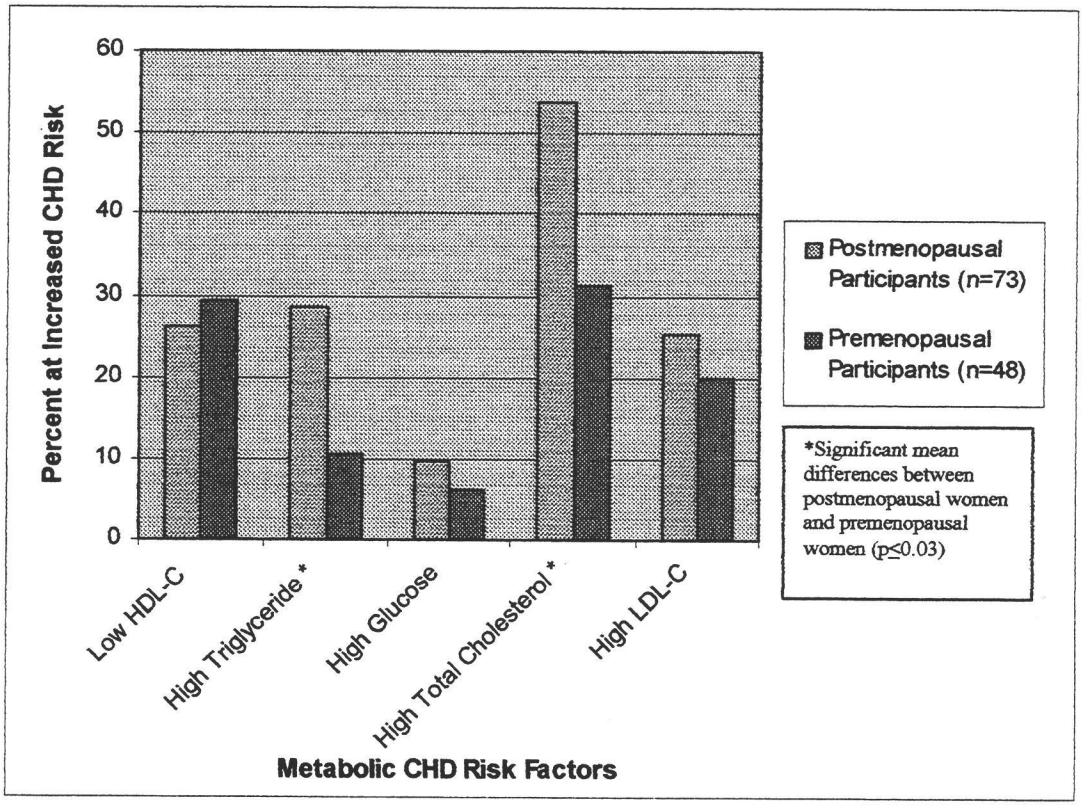

Figure 1.1 displays the data summarizing the frequency of pre- and postmenopausal women at increased CHD risk from metabolic risk factors. Among all postmenopausal participants (n=73), 26% had low levels of HDL-C, 28.4% had high levels of TG, 9.6% had high levels of glucose, 53.7% had high levels of total cholesterol, and 25.4% had high levels of LDL-C. Among all premenopausal participants (n=48), 29.2% had low levels of HDL-C, 10.4% had high levels of TG, 6.3% had high levels of glucose, 31.1% had high levels of total cholesterol, and 20% had high levels of LDL-C. Mean levels of total cholesterol (p=0.03) and TG (p=0.002) were significantly lower in premenopausal women relative to postmenopausal women.

Figure 1.2: Frequency of Postmenopausal Participants at Increased CHD Risk from Metabolic Risk Factors

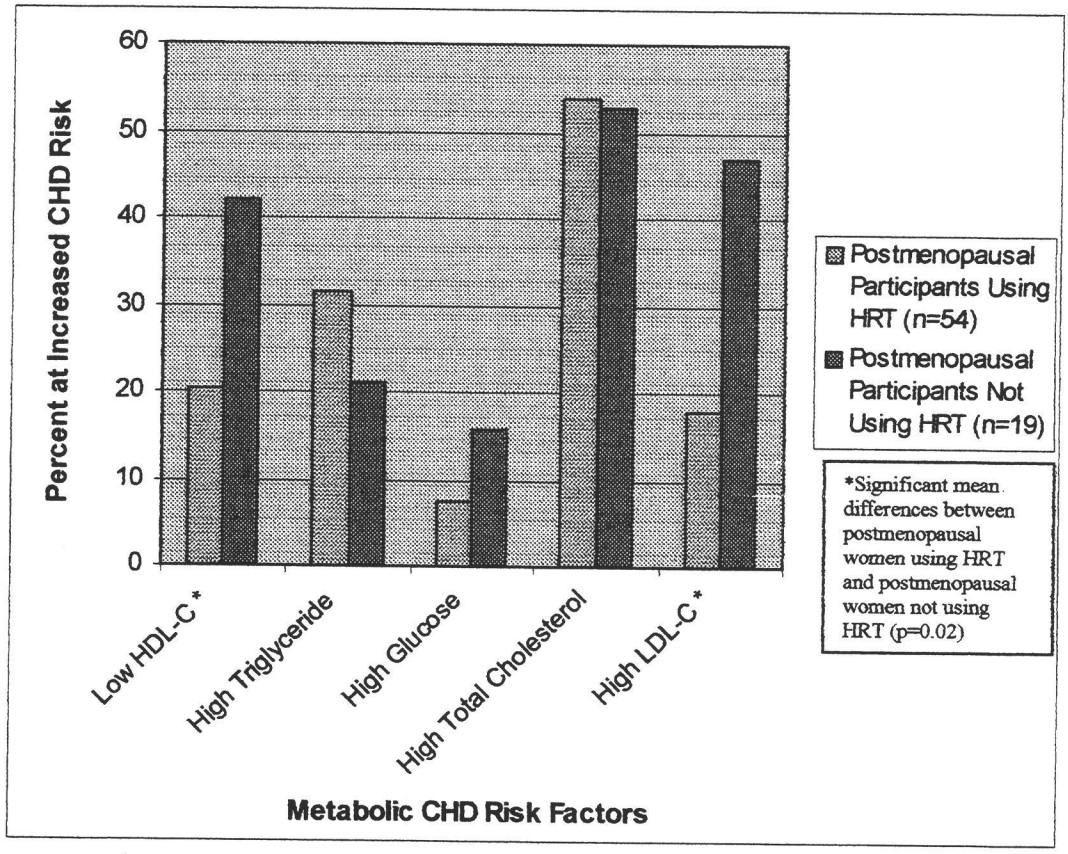

Figure 1.2 displays the data summarizing the frequency of postmenopausal women using and not using HRT at increased CHD risk from metabolic risk factors. Postmenopausal women using HRT (n=54) had more favorable metabolic CHD–risk factor profiles than postmenopausal women not using HRT (n=19). Mean HDL-C levels were significantly higher (p=0.02) and mean LDL-C levels were significantly lower (p=0.02) in postmenopausal women using HRT relative to postmenopausal women not using HRT, but no significant differences were observed in mean levels of TG, total cholesterol, or glucose between postmenopausal women using HRT and postmenopausal women not using HRT. Approximately 42% of postmenopausal women not using HRT had low HDL-C levels, while only 20% of postmenopausal women using HRT had low HDL-C levels. In contrast, high TG levels were more frequent among postmenopausal HRT users (31.5%) than postmenopausal HRT

nonusers (21%). The frequency of high total cholesterol levels was similar between postmenopausal HRT users and postmenopausal HRT nonusers (~53%), but the frequency of high LDL-C levels was greater in postmenopausal women not using HRT (47%) relative to postmenopausal women using HRT (18%).

Figure 1.3: Frequency of Premenopausal Participants at Increased CHD Risk from Metabolic Risk Factors

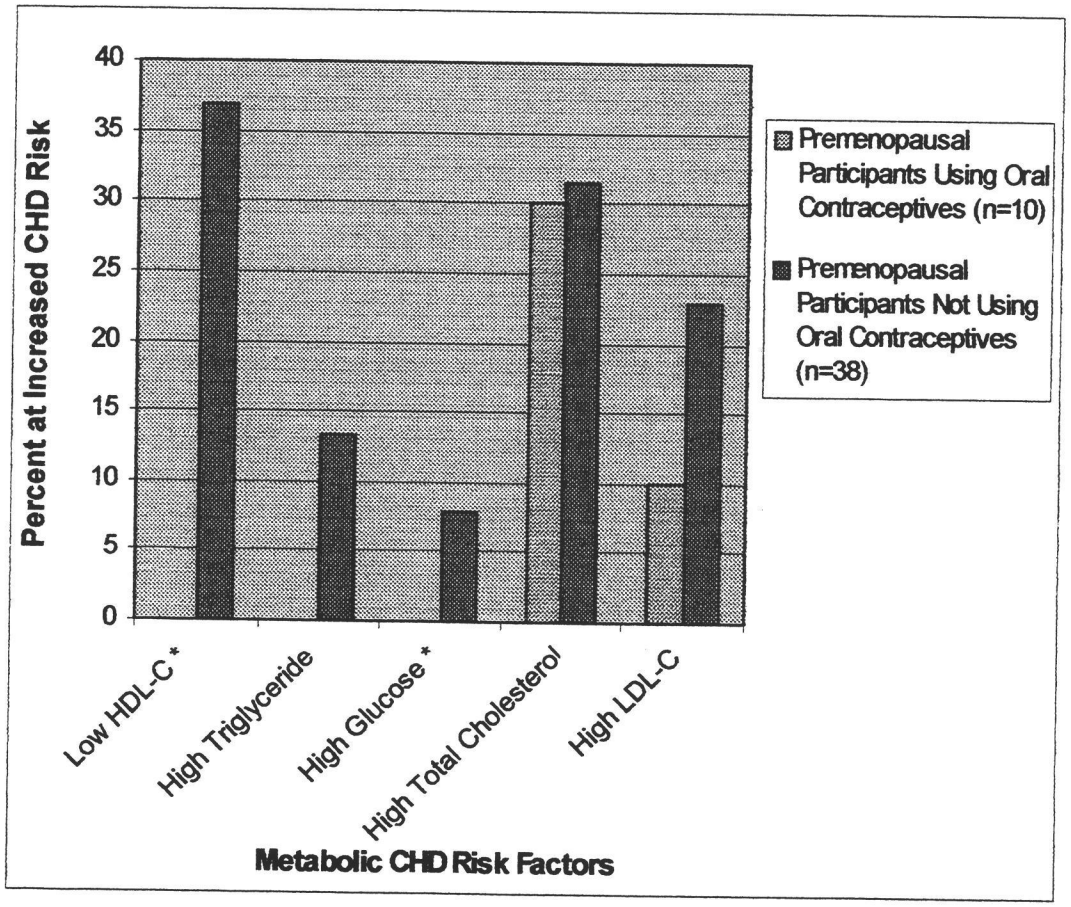

Figure 1.3 displays the data summarizing the frequency of premenopausal women using and not using oral contraceptives at increased CHD risk from metabolic factors. Premenopausal women using oral contraceptives (n=10) had more favorable metabolic CHD–risk factor profiles than premenopausal women not using oral contraceptives (n=38). Mean HDL-C levels were significantly higher (p=0.01) and mean glucose levels were significantly lower (p=0.0001) in premenopausal women

using oral contraceptives relative to premenopausal women not using oral contraceptives, but no significant differences were observed in mean levels of TG, total cholesterol, or LDL-C between premenopausal women using oral contraceptives and premenopausal women not using oral contraceptives. Furthermore, the frequency of low HDL-C levels was 36.8% among premenopausal women not using oral contraceptives, whereas none of the premenopausal women using oral contraceptives had low levels of HDL-C. Similarly, high levels of TG and glucose were evident among premenopausal women not using oral contraceptives (13.2% and 7.9%, respectively), but absent in premenopausal women using oral contraceptives.

DISCUSSION

The majority of women with MS in the present sample adopted several health-related behaviors including regular participation in some form of physical activity, regular use of vitamins, and limited alcohol consumption. The majority of women did exceed recommended intakes of dietary fat, however, and slightly less than half met current recommendations for dietary intakes of vegetables and fruits. Mean levels of dietary intake of total fat intake among study participants are comparable to dietary intake of total fat reported from the general population (≅34%) (43).

The percentage of physically active behaviors in the present sample of women with MS exceeds the percentage of physically active behaviors reported in the general population of women participating in the BRFSS and contradicts previous research which suggests that women with MS have low participation in LTPA (76,87). In this regard, 65% of women in the present sample regularly participated in light- to moderate-intensity LTPA, 10.6% regularly participated in vigorous-intensity LTPA, 68.3% met LTPA recommendations described in the 1996 BRFSS (i.e., regular participation in any intensity of LTPA), and 31.7% irregularly or never participated in LTPA. By contrast, 22% of women with MS have been reported to regularly participate in light- to moderate-intensity LTPA (114) and the 1996 BRFSS estimates that 23.1% of women in the United States regularly participate in light- to moderate-intensity LTPA, 15.4 % regularly participate in vigorous-intensity LTPA, 28.4% meet LTPA recommendations, and 71.5% irregularly or never participate in LTPA.

Several explanations may be responsible for the high frequency of reported LTPA in this sample. For instance, because 85% of women participating in the present study were ambulatory, the higher levels of LTPA in this sample relative to the levels of LTPA previously described in women with MS (76,87) may be accounted for by greater mobility and less disability observed in the present sample. In addition, because the study was promoted as a health behavior study, it is likely that the present sample was somewhat biased towards more health conscious women. It is important to emphasize, however, that not all nonambulatory women were inactive. In fact, five nonambulatory women regularly participated in light physical activity and seven ambulatory women

were inactive during their leisure-time. Furthermore, ten women who required aids for ambulating regularly participated in light-intensity LTPA and five women who required aids for ambulating regularly participated in moderate-intensity LTPA.

The majority of women in this study regularly participated in light- to moderate-intensity LTPA (65%), but few participated in vigorous-intensity LTPA (10.6%). Less participation in light- to moderate-intensity LTPA (23.1%), but greater participation in vigorous-intensity LTPA (15.4%), however, was reported by women screened in the BRFSS relative to women in the present sample. The high frequency of gardening activity among study participants (50.4%) relative to the frequency of gardening activity described in women from the NHIS (25.1%) may be explained by the period of data collection. In the present study, participants were asked to describe their participation in LTPA during the preceding week. Because data was collected in the summer, the frequency of gardening activities was high. In the NHIS, participants were asked to describe their participation in LTPA during the preceding two weeks. Because the NHIS screens subjects year-round, the frequency of seasonal activities, such as gardening, are systematically underestimated in persons not screened in the spring and summer. Therefore, it is difficult to accurately compare gardening behaviors between those participating in this study and those participating in the NHIS.

The large proportion of women meeting the recommended levels of LTPA in this sample can also be explained by the new duration requirements described in the 1996 BRFSS, which allows light- to moderate-intensity LTPA to be accumulated in 10 minute continuous bouts as opposed to 30 minutes of sustained, continuous activity required in previous BRFSS. These requirements are more feasible and attainable by women with MS who may overheat and fatigue with physical activity bouts of greater duration.

Despite the high participation in LTPA among study participants, more than half of participants had total body fat (69.1%) and abdominal circumferences (52%) exceeding values recommended for health. Based on BMI, almost 50% of the women were overweight and half of these overweight women were obese according to standards established by the World Health Organization (135). The frequency of overweight and obesity in this sample is slightly less, but comparable to the frequency

of overweight and obesity reported in women participating in the NHANES III (i.e., 55%, overweight; 27%, obese) (38), which places our participants at similar risk for medical complications arising from excess weight as the general population of women without MS. Nevertheless, the similarities in the occurrence of overweight and obesity between our findings and those reported from the NHANES III should not mistakenly lead us to believe that the prevalence of overweight and obesity in women with MS is not of considerable concern. Rather, the findings contribute to the recent literature exposing the alarming rate at which overweight and obesity are increasing in the American population. Obesity and, in particular, abdominal obesity, are strongly related to, and frequently precede the onset of hypertension, noninsulin dependent diabetes mellitus (NIDDM), and CHD (21,57,88,96,98). Thus, almost half of the women in the current study are at increased risk for hypertension, NIDDM, and CHD. Furthermore, 16% of the participants had waist circumferences exceeding 96.5 cm, which more than triples their risk for experiencing a CHD-related event (101). The economic cost associated with the treatment of adiposity-related illness in overweight and obese women with MS only adds to the existing health care burden associated with the treatment and management of MS-related disorders.

The frequency of high levels of TG ($\geq$200 mg/dL) and low levels of HDL-C ($\leq$50 mg/dL) among the present sample of women with MS (i.e., 21.5% and 27.3%, respectively) is comparable to the frequency of high levels of TG (19.8%) and low levels of HDL-C (27.7%) reported in women participating in the Lipids Research Clinics' Follow-up Study (72). Findings from the Lipids Research Clinics Follow-up Study identify women with HDL-C levels less than 50 mg/dL at threefold greater risk for cardiovascular disease death relative to women with HDL-C levels exceeding 50 mg/dL (72). Thus, more than 25% of women with MS participating in the current study are at markedly increased risk for cardiovascular disease. It should be noted that some research suggests that TG levels greater than 150 mg/dL are associated with substantial increased risk for CHD (15). In the current sample, 43.8% had TG levels greater than 150 mg/dL. Most importantly, 11.5% of participants had low HDL-C levels in combination with high TG levels, which places them at an eightfold increased risk for cardiovascular disease death (72).

Premenopausal women had significantly lower levels of total cholesterol and TG relative to postmenopausal women. Consistent with data reported from major HRT intervention trials examining CHD risk between postmenopausal women using and not using HRT (52,136), the present sample of postmenopausal women with MS using HRT had significantly higher levels of HDL-C and significantly lower levels of LDL-C relative to postmenopausal women with MS not using HRT. Moreover, the percentage of postmenopausal women not using HRT having low HDL-C levels (42.1%) and high glucose levels (15.8%) was doubled relative to the percentage of postmenopausal women using HRT (20.3% and 7.4%, respectively). HRT use is frequently reported to raise TG levels (52,136). Although there was a greater percentage of postmenopausal women using HRT having high levels of TG (31.5%) relative to postmenopausal women not using HRT (21%), no significant differences in mean TG levels were observed between postmenopausal women using and not using HRT in the present study.

High levels of LDL-C are not considered to be as strong a risk factor for CHD as low levels of HDL-C in women (72). The lower percentage of high LDL-C levels in the sample of postmenopausal women using HRT, however, should be appreciated. In this regard, the percentage of postmenopausal women not using HRT having LDL-C levels exceeding values recommended for metabolic health (47%) was 2.5 times greater than observed in postmenopausal women using HRT (18%).

Oral contraceptives are reported to unfavorably raise levels of TG and glucose, and lower levels of HDL-C (15). The frequencies of high levels of TG (13.2%) and glucose (7.9%), and low levels of HDL-C (36.8%) were evident in premenopausal women not using oral contraceptives, however, but absent in premenopausal women using oral contraceptives. Moreover, premenopausal women using oral contraceptives had significantly higher levels of HDL-C and significantly lower levels of glucose relative to premenopausal women not using oral contraceptives.

In summary, the frequency of participation in LTPA physical activity was high in this sample of women with MS and may be explained by the following: 1.) the majority of activities reported were light- to moderate-intensity LTPA and 2.) the present sample consisted of more functional, less disabled, and perhaps, more health-

conscious women with MS. Thus, it is reasonable to believe that more disabled and less health-conscious women with MS may be less physically active than those participating in this study, and may, therefore, be at greater risk for CHD than women participating in this study. Still, the high prevalence of physically active behaviors among our participants provides promising hope that women with MS can remain physically active "within the context of their disability (114)."

Despite the high participation in LTPA, women with MS in this sample were at similar CHD risk as the general population of women without MS with respect to body composition and levels of TG and HDL-C. The relationship between physical activity and CHD risk is complicated, however, and influenced by other factors including dietary intake of total fat, which may interfere with the positive effects that physical activity has on improving CHD risk. In this regard, almost 70% of women had dietary intakes of total fat exceeding recommended levels. High dietary intake of fat may contribute to higher levels of adiposity and unfavorable levels of the metabolic CHD risk factors, and must be considered with respect to the frequency of anthropometric and metabolic CHD risk factors observed in this sample.

Because CHD risk is the leading cause of death in women in the United States, the similarities in CHD risk between our findings and those reported in the general population of women emphasize the importance of improving health behavior practices and identifying effective and attainable preventative measures for reducing CHD risk in women with and without MS. The development and implementation of strategies aimed at improving health behavior practices, in particular, physical activity, is uniquely challenging in women with MS given the limitations and fatigue imposed by their disability. Nevertheless, adoption of better health behaviors can reduce CHD risk, and most importantly, improve the quality of life in women with MS, such that "good or poor health can exist in the presence or absence of overt illness or disability (114)."

DIFFERENCES IN CORONARY HEART DISEASE RISK FACTORS BETWEEN ACTIVE AND INACTIVE WOMEN WITH MULTIPLE SCLEROSIS

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ABSTRACT

Background: The United States Surgeon General emphasizes the need for research focusing on preventative measures for reducing coronary heart disease (CHD) risk, specifically in women and those with disabilities. Physical activity is strongly recommended as a principal component of CHD-risk factor management aimed at favorably lowering abdominal fat accumulation, lowering levels of triglyceride (TG), raising levels of high-density lipoprotein-cholesterol (HDL-C), and improving insulin sensitivity. Although physical activity practices are reported to be low in women with multiple sclerosis (MS), some women with MS remain physically active despite their disability. Thus, the primary aim of the study was to determine whether abdominal fat accumulation and levels of TG, HDL-C, and glucose differ between active and inactive women with MS.

Methods: The study sample consisted of 123 women with MS, aged 23 to 72 years. Venous blood was collected for measurement of lipids, lipoprotein-cholesterol, and glucose. Skinfold thicknesses and girth circumferences were obtained for estimation of total and abdominal body fat. Leisure-time physical activity (LTPA) during the last 12 months was assessed by the physical activity questionnaire used in the Postmenopausal Estrogens/Progestins Intervention Study. Eating habits were assessed by the Block Food Frequency Questionnaire.

Results: LTPA was significantly associated with lower waist circumference ($p=0.0001$), lower TG levels ($p=0.0005$), lower glucose levels (0.002), and marginally with higher HDL-C levels ($p=0.09$). After adjusting for the covariates (age, hormone replacement therapy and oral contraceptive use, current and past cigarette use, and alcohol intake), women participating in low- to moderate-intensity LTPA had significantly lower waist circumferences, TG levels, and glucose levels relative to inactive women.

Conclusions: Low- to moderate-intensity LTPA was significantly associated with less abdominal fat accumulation, lower levels of TG and glucose, and to some extent higher levels of HDL-C in the present sample of women with MS. These findings suggest that exercise levels attainable by women with MS may improve CHD risk and contribute to important health-related benefits.

INTRODUCTION

Women are twice as likely to develop MS than men (87,113). With the continual development of new medications for the treatment of MS, women with MS are living longer, which in turn increases their risk for developing age-related secondary chronic conditions, including CHD (89,105,113). Moreover, because women with MS frequently have low participation in physically active behaviors (76,114), and because physical inactivity is designated as a major CHD risk factor (36,82,123), women with MS may be at additional risk for CHD as they age. In fact, physically inactive individuals have a twofold increased risk for CHD mortality relative to their physically active counterparts (82).

Physical inactivity raises CHD risk, in part, by its association with greater abdominal fat accumulation, higher levels of TG, lower levels of HDL-C, and reduced insulin sensitivity, which is represented by high circulating levels of insulin and glucose (21,36,123). High circulating levels of TG ($\geq$ 200 mg/dL) and low circulating levels of HDL-C ($\leq$ 50 mg/dL) are strong independent biological predictors of CHD risk in women (20,72). Reduced insulin sensitivity causes circulating levels of glucose to rise and is frequently associated with high circulating levels of TG and low circulating levels of HDL-C (21,24,57). Furthermore, increasing amounts of abdominal fat are believed to precede and be largely responsible for reduced insulin sensitivity and unfavorable circulating levels of TG and HDL-C (21,24,88).

Participation in LTPA is avoided by many women with MS (114). Some women with MS, however, remain physically active despite their disability. At present, it is unknown whether women with MS are able to participate in enough physical activity to achieve health-related benefits and to reduce their risk for CHD. Thus, *the primary aim of the study was to assess the differences in abdominal fat accumulation and levels of TG, HDL-C, and glucose between women with MS participating in higher intensity LTPA and inactive women with MS.* The primary aim was intended to determine what intensity of LTPA might be necessary to reduce CHD risk in women with MS. It was hypothesized that women reporting participation in increasing intensities of LTPA would have more favorable CHD-risk factor profiles than women

reporting no participation in LTPA. In addition, because physical activity–related improvements in the metabolic CHD risk factors are suggested to be mediated through physical activity–related reductions in total and abdominal fat, *the present, cross-sectional study evaluated whether the association between LTPA and the metabolic CHD risk factors was independent from levels of total and abdominal fat in the sample of women with MS.*

METHODS

Official approval for the research project was granted by Oregon State University, Corvallis; Rogue Valley Medical Center, Medford; and Oregon Health Sciences University, Portland. The Institutional Review Board proposal is included in appendix A. Data was collected from the MS clinic at Oregon Health Sciences University, the Health and Human Performance Lab at Oregon State University, the Asante Health Promotion offices at Rogue Valley Medical Center, the Springfield Willamalane Senior Activity Center, the Three Rivers Hospital in Grants Pass, and the Salem Hospital Rehabilitation Center. An informed consent was completed by each participant prior to data collection. The informed consent form is included in appendix B.

Women volunteers were recruited from Oregon MS chapters, physician referrals, and newspaper announcements. Women with diagnosed cardiovascular disease, insulin-treated diabetes, gout, or recently diagnosed thyroid disorder, and women who currently used oral prednisone, smoked more than ten cigarettes per day, or consumed more than four alcoholic beverages per day were excluded. Three women were using cholesterol-lowering medications. Excluding these women from the present analyses did not appreciably alter any of the results. All subjects had physician-diagnosed MS.

Assessment of Lipids, Lipoprotein-Cholesterol, and Glucose

Venous blood (< 10 ml) was collected by venipuncture following a 12-hour fast by trained lab technicians using sterile procedures. Firm pressure and a bandage was applied to the venipuncture site immediately following blood collection. Serum and red blood cells were separated by centrifugation at 1900 x g for 15 minutes. The serum was transferred to plastic, labeled vials and frozen at -70° C for later analysis of lipid/lipoprotein-cholesterol (total cholesterol, TG, HDL-C, and low-density lipoprotein-cholesterol (LDL-C)) and glucose concentrations by Rogue Valley Medical Center.

Quality control of the Rogue Valley Medical Center laboratory is monitored by the Lipid Standardization Program of the Centers for Disease Control and Prevention. Measurements of lipid/lipoprotein-cholesterol and glucose were within specific limits established by the Lipid Standardization Program of the Centers for Disease Control and Prevention (i.e., 2.6 SD, 1.23% CV for total cholesterol; 2.3 SD, 1.41% CV for TG; 1.2 SD, 1.89% CV for HDL-C; and 1.2 SD, 3.26% CV for glucose).

Total cholesterol concentrations were determined by enzymatic procedures in serum with cholesterol esterase, cholesterol oxidase, and peroxidase, which produce colored products that are analyzed with spectrophotometers (125). TG concentrations were determined by enzymatic procedures in serum with glycerol kinase, glycerolphosphate oxidase, and peroxidase. Again, colored products produced are spectrophometrically analyzed (125). HDL-C levels were determined using the direct EZ-HDL Sigma assay, which uses anti human 9-lipoprotein antibody to bind with LDL, VLDL, and chylomicrons. HDL-C levels can then be directly analyzed by enzymatic procedures previously described for total cholesterol. High correlations are reported for HDL-C levels between the Sigma method and standard enzymatic methods used after precipitation of beta lipoproteins with magnesium/dextran sulfate ($r=0.98$). After directly measuring the concentrations of total cholesterol, TG, and HDL-C, LDL-C can be calculated indirectly with the Friedwald equation (40):

$$\text{LDL-C} = \text{Total cholesterol} - \text{HDL-C} - \text{TG}/5$$

Glucose concentrations were determined by an oxygen rate method with a Beckman Oxygen electrode. After adding glucose oxidase to the glucose sample, electronic circuits measure the oxygen consumption rate, which is directly proportional to the glucose concentration in the sample.

Because blood samples were initially going to be analyzed by Dr. Rosemary Wander's Lipid Laboratory at Oregon State University, all samples were collected in plasma EDTA tubes during the first week of testing. There was, however, an unexpected early closure and relocation of Dr. Wander's Lipid Laboratory before all blood samples could be collected. Although the laboratory at Rogue Valley Medical Center agreed to analyze the blood samples for lipid/lipoprotein-cholesterol and glucose concentrations, the laboratory was unable to accurately determine total cholesterol from

samples collected in plasma EDTA tubes, estimating ≤24% bias. The majority of the participants returned the following week to have their blood recollected in serum separator tubes so that their total cholesterol levels could be analyzed by the Rogue Valley Medical Center laboratory. Values for total cholesterol and LDL-C are missing from nine subjects who participated in the study during the first week of data collection but were unable to return for a blood redraw. Because the methods used by the Rogue Valley Medical Center laboratory could accurately determine levels of TG, HDL-C, and glucose obtained in the plasma EDTA tubes, concentrations of TG, HDL-C, and glucose from the nine subjects who did not return for a blood redraw were included in the data analysis. We were unable to obtain blood samples from two subjects. Thus, all measurements of lipid/lipoprotein-cholesterol and glucose are missing from these two subjects. Finally, because the Friedwald equation, which is used to calculate LDL-C from total cholesterol, HDL-C, and TG, is invalid when TG levels exceed 400 mg/dL, LDL-C levels are missing from two subjects who had TG levels greater than 400 mg/dL.

Anthropometry for Assessment of Total and Abdominal Fat

Body weight was measured with a standard balance-beam scale in light clothing without shoes at the Corvallis, Portland, Medford, and Grants Pass testing sites, and with a digital scale at the Springfield and Salem testing sites. For participants who were unable to stand, body weight was obtained on a chair scale when feasible. Three participants were weighed on a chair scale. Weight was not obtained for five nonambulatory participants. An estimate of weight for these five participants was obtained from their physician. Height was measured without shoes using a stadiometer. For participants tested at locations which lacked a stadiometer, and for participants who were unable to stand, they were asked to contact their physician for their height. Measurements (and estimates) of weight and height were used to calculate body mass index.

Waist and hip circumferences were measured with a tape measure. Waist circumference was measured at the narrowest portion of the torso between the top of the

iliac crest and the lowest rib. Hip circumference was measured at the level of the greater trochanter. Continuous measurements of girth circumferences were conducted in rotational order until measurements were within 1 cm agreement. For the participants who were unable to stand, girth circumferences were measured in a reclining position when feasible. The average of waist and hip circumferences within 1 cm agreement were used to calculate the waist to hip ratio. The waist circumference was used as the primary index for abdominal obesity in the data analyses because it is considered to be the most accurate anthropometric measure of abdominal and visceral obesity (91).

Total body fat was calculated from multicomponent prediction equations using skinfold thicknesses as an estimate of subcutaneous fat (127). Skinfold thicknesses were measured with a Lange skinfold caliper at four sites on the right side of the body (triceps, subscapular, abdomen, and calf) according to standardized procedures (49). To reduce standing time for the participants, however, skinfold measurements for the triceps, subscapular, and calf were obtained in a sitting position. Abdominal skinfold measurements were obtained in a standing position. For the participants unable to stand, abdominal skinfold measurements were obtained in a reclining position. Continuous measurements of skinfold thicknesses were conducted in rotational order until measurements for each site were within 1 mm agreement. The sum of the 4 skinfold sites were used in the following multicomponent prediction equation for women (127).

$$\%BF = 0.428(\text{sum skinfolds}) - 0.0011(\text{sum of skinfolds}^2) + 0.127(\text{age}) - 3.01$$

The multicomponent prediction equations used in the present study were chosen because 1.) they were developed on women between the ages of 34 and 84, 2.) they account for individual differences in the mineral and water components of fat free mass, 3.) they yield high multiple correlation coefficients between skinfold thicknesses and body fat (ranging from 0.88 to 0.91) and small standard error estimates (ranging from 2.6 to 3.2), and 4.) they have been used previously in the literature to estimate body fat specifically in women with MS (86).

Physical Activity Assessment

The physical activity questionnaire used in the Postmenopausal Estrogens/Progestins Intervention (PEPI) Study (42) was administered to assess occupational, home, and leisure-time physical activity during the last 12 months. Participants were asked to classify their intensity of occupational, home, and leisure-time physical activity into inactive, light, moderate, and heavy categories based on the examples provided. The criteria for intensity of physical activity is comparable to the criteria for intensity of physical activity established by the Centers for Disease Control and Prevention (82). A copy of the physical activity questionnaire from the PEPI Study is included in appendix F.

Diet Composition

Eating habits and diet composition were assessed by the Block Food Frequency Questionnaire (BFFQ). The BFFQ provides valid and reliable information regarding dietary intake of total fat, saturated fat, and nutritional supplements (8). The BFFQ was analyzed by Block Dietary Data Systems. A copy of the BFFQ is included in appendix D.

Medical History

Because hormone replacement therapy (HRT) use, oral contraceptive use, smoking history, alcohol consumption, and some medications are known to influence the metabolic CHD risk factors (36,109), a brief medical history questionnaire was administered to obtain important information regarding medication use and personal habits of study participants in order to control for such potential confounders in the data analysis. A brief mobility questionnaire (64) was included in the medical history questionnaire to obtain information regarding the level of disability among study participants, so that the associations between physical disability and physical activity practices could be examined. Physical disability ranged from a rating of 1 (I have no

restriction on activities of normal employment or domestic life, but I am not necessarily symptom free) to a rating of 7 (I must be in bed all or most of the time). A copy of the medical history questionnaire is included in appendix E.

Statistics

Before running the statistical analysis, pairwise scatter plots were made to assess linearity, homoscedasticity, and the presence of outliers. Because the frequency distribution of TG levels was skewed, TG levels were scaled using the natural log transformation prior to running the statistical analyses. General linear models were used to test for relationships between each physical activity measure and the selected CHD risk factors (abdominal circumference, TG, HDL-C, and glucose). Multivariable models included age, HRT and oral contraceptive use, current and past cigarette use, and alcohol consumption. The following general model was fit using the General Linear Model Procedure in SAS (v6.12) to each CHD risk factor:

CHD risk factor = mu + beta1(age) + beta2(HRT use) + beta3(oral contraceptive use) + beta4(past cigarette use) + beta5(current cigarette use) + beta6(alcohol use) + beta7(physical activity2) + beta8(physical activity3) + beta9(physical activity4) + episilon

where:
physical activity 2 = light physical activity
physical activity 3 = moderate physical activity
physical activity 4 = heavy physical activity
CHD risk factor = abdominal circumference, TG, HDL-C, glucose
epsilon = error term
mu = intercept term

Age was a continuous variable. HRT and oral contraceptive use, current and past cigarette use, alcohol use, and physical activity were categorical variables. All of the noncontinuous variables were treated as categorical variables. All covariates were included into the model before adding physical activity. The four categorical physical activity variables were regressed on the residuals from the model with just the covariates known to influence the CHD risk factors in order to account for unforeseen relationships and to reduce problems arising from multicollinearity. Statistically

significant F tests observed for the association between the CHD risk factors and the levels of physical activity indicated that the mean levels of the CHD risk factors were different across the different levels of physical activity after adjusting for the covariates. The Fischer Protected Least Significant Difference procedure was used to determine which physical activity levels were different from each other while controlling for the type I error rate (14).

For relationships that were significant between the physical activity measures and the metabolic CHD risk factors after adjusting for the covariates, total body fat (continuous variable) and waist circumference (continuous variable) were added as covariates separately into the models to determine whether the associations between physical activity and more favorable levels of the metabolic CHD risk factors were influenced by lower amounts of total and abdominal fat. Dietary intake of fat (continuous variable) was also added as a covariate into the original significant models to determine whether differences in dietary intake of fat among participants influenced the interpretations regarding the true association between physical activity and the metabolic CHD risk factors.

RESULTS

Table 2.1 shows that women reporting greater participation in higher intensity LTPA during the last 12 months were more likely to adopt other health-related behaviors, including significantly lower dietary intakes of total fat (p=0.01), marginally lower dietary intakes of saturated fat (p=0.06), significantly higher daily intakes of vegetables (p=0.03) and fruits (p=0.008), and significantly greater use of multivitamin/antioxidant supplements (p=0.003). Mobility was inversely associated with LTPA (p=0.001), total body fat (p=0.03) (data not shown), and waist circumference (p=0.0001) (data not shown), indicating that women with greater mobility and less disability were more likely to participate in higher intensity LTPA and were more likely to have lower amounts of total and abdominal fat. Cigarette and antidepressant use were not related to LTPA.

Table 2.1: Relationship between Leisure-Time Physical Activity (LTPA) and Age, Diet, Smoking, Alcohol, Medication Use, and Mobility in Participants.

Variable	LTPA				P Value
	Inactive (n=19)	Light (n=47)	Moderate (n=40)	Heavy (n=17)	
Age (yr)	53.4	50.7	48.9	45.8	0.01
Dietary Behaviors					
Total Fat Intake (%)	35.7	34.0	33.9	28.4	0.01
Saturated Fat Intake (%)	9.7	9.4	9.6	7.1	0.06
Vitamin Use (%)	58	81	82	100	0.003
Vegetable Intake (servings/day)	2.9	3.6	3.3	5.3	0.03
Fruit Intake (servings/day)	1.7	1.9	1.9	2.9	0.008
Cigarette Use					
Current (<10/day) (%)	0	11	5	0	0.63
Past (%)	37	43	25	24	0.16
Alcohol Intake (%)	5	32	35	41	0.02
Medication Use					
Antidepressant (%)	42	47	30	29	0.17
Postmenopausal HRT (%)	37	50	48	35	0.84
Premenopausal OC (%)	0	8.5	5	23.5	0.05
Mobility	4.5	2.2	1.5	1.3	0.001

HRT, Hormone Replacement Therapy
OC, Oral Contraceptive

Table 2.2 shows that women reporting greater participation in higher intensity physical activity had more favorable levels of adiposity for all indices of body composition (i.e., body mass index, waist circumference, waist to hip ratio, and body fat), significantly lower TG levels (p=0.0005), significantly lower glucose levels (p=0.002), and marginally higher HDL-C levels (p=0.09). Work and home activity during the last 12 months were not significantly associated with any of the CHD risk factors.

Table 2.2: Mean Values for Adiposity, Lipids, Lipoprotein-Cholesterol, and and Glucose by Intensity of Leisure-Time Physical Activity (LTPA).

Variable	LTPA				P-Value
	Inactive (n=19)	Light (n=47)	Moderate (n=40)	Heavy (n=17)	
Adiposity					
Body Mass Index (kg/m^2)‡	30.4	26.0	26.0	23.1	0.002
Waist Circumference (cm)*	92.6	82.7	80.4	74.8	0.0001
Waist to Hip Ratio**	0.80	0.76	0.75	0.75	0.004
Body Fat (%)*	41.3	37.6	37.2	30.8	0.0002
Metabolic Variables					
Triglyceride (mg/dL)†	187.6	164.0	123.2	120.0	0.0005
HDL-C (mg/dL)†	54.1	62.0	61.6	63.1	0.09
Glucose (mg/dL)†	100.9	91.4	90.9	88.4	0.002
Total Cholesterol (mg/dL)††	209.3	205.8	184.3	198.5	0.06
LDL-C (mg/dL)††	117.7	109.4	98.5	112.5	0.27

HDL-C, High-density lipoprotein-cholesterol
LDL-C, Low-density lipoprotein-cholesterol

*N=122 because of missing values
†N=121 because of missing values
‡N=120 because of missing values
**N=118 because of missing values
††N=112 because of missing values

After adjusting for age, HRT and oral contraceptive use, current and past cigarette use, and alcohol intake, the relationship between LTPA and waist circumference remained significant (p=0.01) (table 2.3) (figure 2.1). The mean waist circumference for participants in the light (x=81.1 cm), moderate (x=79 cm), and heavy (x=74.2 cm) LTPA groups were significantly lower than the mean waist circumference for participants in the inactive (x=88.9 cm) LTPA group. Additionally, the mean waist

circumference for participants in the heavy LTPA group was significantly lower than the mean waist circumference for participants in the light LTPA group.

The inverse association between LTPA and TG levels remained significant after adjusting for age, HRT and oral contraceptive use, current and past cigarette use, and alcohol intake (table 2.3) (figure 2.1). The mean TG levels for women in the moderate (x=134.4 mg/dL) and heavy (x=137.2 mg/dL) LTPA groups were significantly lower than the mean TG level for women in the inactive (x=194.9) LTPA group. Additionally, the mean TG level for participants in the moderate LTPA group was significantly lower than the mean TG level for participants in the light (x=169.6) LTPA group. TG levels were positively associated with total body fat (p=0.0001) and waist circumference (p=0.0001), and marginally with dietary intake of fat (p=0.07). The statistically significant association between LTPA and TG levels was maintained after including body fat (p=0.03) (table 2.4) and dietary intake of fat into the models (p=0.02) (data not shown), but was lost when waist circumference was included into the model (p=0.14) (table 2.5). The presented means for TG levels across the LTPA levels are not log transformed.

The inverse association between LTPA and glucose levels remained significant after adjusting for age, HRT and oral contraceptive use, current and past cigarette use, and alcohol intake (p=0.02) (table 2.3) (figure 2.1). The mean glucose levels for women in the light (x=87.3 mg/dL), moderate (x=86.4 mg/dL), and heavy (85.5 mg/dL) LTPA groups were significantly lower than the mean glucose level for women in the inactive (x=96.2 mg/dL) LTPA group. Glucose levels were positively associated with total body fat (p=0.0001) and waist circumference (p=0.0002), but not with dietary intake of fat (p=0.17). The statistically significant association between LTPA and glucose was maintained after including total body fat (p=0.03) (table 2.4) and dietary intake of fat into the model (p=0.01) (data not shown), and was barely maintained after including waist circumference into the model (p=0.057) (table 2.5).

Although mean HDL-C levels appeared somewhat higher in those participating in all intensities of LTPA relative to inactive participants, the standard deviations were too large for the differences between the HDL-C means to be significant either before or after adjusting for the covariates (table 2.3) (figure 2.1). Stratification of

postmenopausal women based on HRT use, and stratification of premenopausal women based on oral contraceptive use, did not alter the nonsignificant trend between physical activity and HDL-C levels but almost became significant in premenopausal women not using oral contraceptives (p=0.08).

Table 2.3: Adjusted Mean WC, TG, Glucose, and HDL-C by Intensity of Leisure-Time Physical Activity (LTPA).

LTPA	Adjusted Mean WC(cm)*	Adjusted Mean TG(mg/dL)†	Adjusted Mean Glucose(mg/dL)†	Adjusted Mean HDL-C(mg/dL)†
	p=0.01	p=0.01	p=0.02	p=0.5
Inactive (n=19)	88.9	194.9	96.2	60.7
Light (n=47)	81.1‡	169.6	87.3‡	66.1‡
Moderate (n=40)	79.0‡	134.4‡¶	86.4‡	65.9‡
Heavy (n=17)	74.2‡¶	137.2‡	85.5‡	66.5‡

WC, Waist Circumference; TG, Triglyceride; HDL-C, High-Density Lipoprotein Cholesterol
*N=122 because of missing values
†N=121 because of missing values
Adjusted for age, hormone replacement therapy and oral contraceptive use, current and past cigarette use, and alcohol consumption.
P-values shown underneath the CHD risk factors are for overall F test.
All other p-values are for contrasts of least-squares means estimates.
Type I comparison error rate was controlled by the Protected Least Significant Difference Procedure.
‡$p \leq 0.05$ vs. inactive
¶$p \leq 0.05$ vs. light

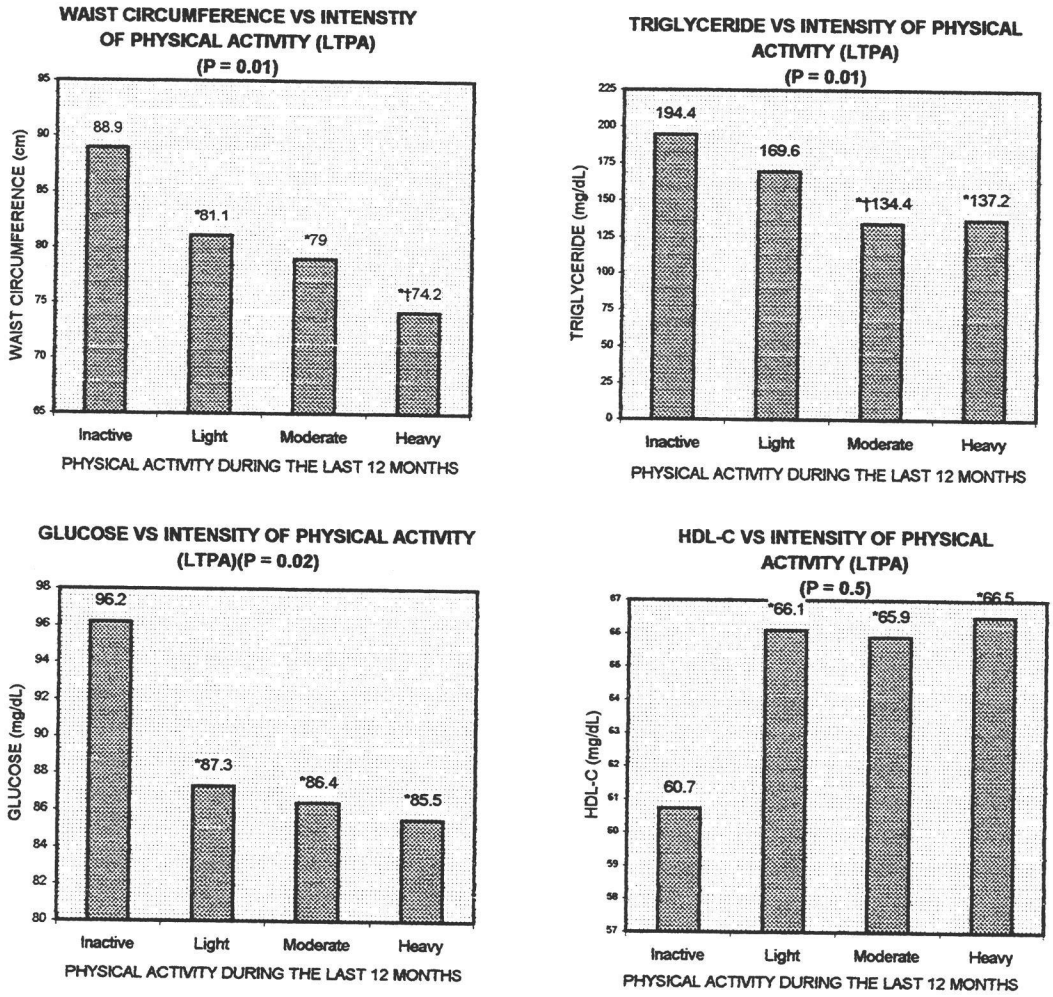


Figure 2.1: Waist Circumference, Triglyceride Levels, Glucose Levels, and High-Density Lipoprotein-Cholesterol (HDL-C) Levels According to the Intensity of Physical Activity during the Last 12 Months

P-values represent the overall F test for the relationship between the CHD risk factors and intensity of physical activity during the last 12 months (LTPA), with adjustment for age, hormone replacement therapy and oral contraceptive use, current and past cigarette use, and alcohol intake. All other p-values are for contrasts of least-squares means estimates: * indicates $p \leq 0.05$ for comparison with the inactive category; † indicates $p \leq 0.05$ for comparison with the light category. Type 1 comparison error rate was controlled by Protected Least Significant Difference.

Table 2.4: Adjusted Mean TG, Glucose, and HDL-C by Intensity of Leisure-Time Physical Activity (LTPA)

LTPA	Adjusted Mean TG (mg/dL)†	Adjusted Mean Glucose (mg/dL)†	Adjusted Mean HDL-C (mg/dL)†
	p=0.03	p=0.03	p=0.58
Inactive (n=19)	188.8	95.9	60.9
Light (n=47)	170.6	87.3‡	66.1‡
Moderate (n=40)	136.0‡¶	86.4‡	65.9‡
Heavy (n=17)	160.5‡¶	86.4‡	65.6‡

TG, Triglyceride; HDL-C, High-Density Lipoprotein-Cholesterol
†N=121 because of missing values
Adjusted for age, hormone replacement therapy and oral contraceptive use, current and past cigarette use, alcohol consumption, and **body fat**.
P-values shown underneath the CHD risk factors are for overall F test.
All other p-values are for contrasts of least-squares means estimates.
Type I comparison error rate was controlled by the Protected Least Significant Difference Procedure.
‡$p \leq 0.05$ vs. inactive, ¶$p \leq 0.05$ vs. light

Table 2.5: Adjusted Mean TG, Glucose, and HDL-C by Intensity of Leisure-Time Physical Activity (LTPA)

LTPA	Adjusted Mean TG (mg/dL)†	Adjusted Mean Glucose (mg/dL)†	Adjusted Mean HDL-C (mg/dL)†
	p=0.14	p=0.057	p=0.82
Inactive (n=19)	212.2	100.8	60.6
Light (n=47)	184.9	92.8‡	64.1‡
Moderate (n=40)	157.8‡¶	92.4‡	63.4‡
Heavy (n=17)	170.4‡¶	92.6‡	62.7‡

TG, Triglyceride; HDL-C, High-Density Lipoprotein-Cholesterol
†N=121 because of missing values
Adjusted for age, hormone replacement therapy and oral contraceptive use, current and past cigarette use, alcohol consumption, and **waist circumference**.
P-values shown underneath the CHD risk factors are for overall F test.
All other p-values are for contrasts of least-squares means estimates.
Type I comparison error rate was controlled by the Protected Least Significant Difference Procedure.
‡$p \leq 0.05$ vs. inactive, ¶$p \leq 0.05$ vs. light

DISCUSSION

This study showed that intensity of LTPA over the past year was related to less abdominal fat accumulation, lower levels of fasting TG and glucose, and marginally with higher levels of fasting HDL-C in a sample of women with MS. Although it is undisputed that physical activity contributes to important health benefits, the exact amount and intensity of physical activity required to achieve these health benefits is unclear. The findings suggest that all intensities of LTPA (light, moderate, heavy) are significantly associated with reduced CHD risk in women with MS. In this regard, significantly lower waist circumferences, TG levels, and glucose levels, and marginally higher HDL-C levels were observed in women reporting participation in light- to moderate-intensity LTPA relative to their sedentary counterparts. Moving from light to moderate or heavy forms of LTPA conveyed additional benefits with respect to waist circumference and TG levels. Adjusting for the covariates (age, HRT and oral contraceptive use, current and past cigarette use, and alcohol intake) slightly attenuated the significant association between LTPA and waist circumference, TG levels, and glucose levels, but the significant trends and overall statistical significance was maintained.

More favorable levels of adiposity were observed with each increase in intensity of LTPA. This suggests that reductions in adiposity accrue with greater participation in increasing intensity of physical activity. Still, the greatest magnitude of difference in body mass index, waist circumference, and the waist to hip ratio was evident between women reporting participation in light-intensity LTPA and women reporting no participation in LTPA. Although interpretations are limited by the cross-sectional design of the present study, the significant associations between LTPA and all indices of total and abdominal adiposity suggest that physical activity may be an effective means for lowering total and abdominal fat.

Greater amounts of abdominal fat are consistently reported to be associated with higher levels of fasting TG (13,25) and glucose (65), and lower levels of fasting HDL-C (13,17,25). Our data agree with these observations in that waist circumference was associated with each of the selected metabolic CHD risk factors (TG, glucose, and

HDL-C). Reductions in physical activity and energy expenditure are believed to contribute to abdominal fat accumulation (21), which in turn is believed to precede and be largely responsible for increases in circulating levels of TG and glucose, and decreases in circulating levels of HDL-C (21,24). In the present sample of women with MS, waist circumference was significantly inversely associated with LTPA. Although the lowest waist circumferences were observed in women reporting heavy-intensity LTPA, women reporting regular participation in light- and moderate-intensity LTPA had significantly lower waist circumferences than those reporting no participation in LTPA. Similarly, low-intensity physical activity has been shown to be associated with lower waist circumferences in older adults (85) and viscerally obese older adults (84).

The current recommendations from the National Cholesterol Education Program (36), which encourage physical activity as an effective means for lowering TG levels, are validated by evidence from several observational and training studies demonstrating an inverse association between physical activity and TG levels (7,31,132,133). In this study, women reporting moderate- and heavy-intensity LTPA had significantly lower TG levels compared with women reporting no LTPA, and women reporting moderate-intensity LTPA had significantly lower TG levels compared with women reporting light-intensity LTPA. The more favorable levels of TG with physical activity are believed to be primarily mediated through an exercise-induced increase in lipoprotein lipase activity that facilitates TG breakdown within circulating chylomicrons and very low-density lipoproteins (10,31,41).

Women reporting participation in any intensity of LTPA had significantly lower glucose levels relative to women reporting no participation in LTPA. The lower glucose levels observed in women participating in either light, moderate, or heavy LTPA suggest that physically active women with MS have improved insulin sensitivity and glucose tolerance. Furthermore, an improved insulin sensitivity may be mechanistically linked with the lower TG levels observed in the present sample of active women, by its association with greater lipoprotein lipase activity (7,43). Our results support findings from the Insulin Resistance Atherosclerosis Study (69), a large cross-sectional study, which observed greater insulin sensitivity among nonvigorously active men and women relative to their inactive counterparts, and findings from the

Nurses Health Study (51), a large prospective study, which observed an inverse association between nonvigorous physical activity and the development of noninsulin dependent diabetes mellitus (NIDDM) in female nurses. In the Insulin Resistance Atherosclerosis Study and the Nurses Health Study, however, moderate- to vigorous-intensity physical activity conferred even greater benefits with respect to insulin sensitivity and NIDDM risk, respectively, than lower-intensity physical activity. By contrast, the present study observed that active women with MS had similar levels of glucose independent from the intensity by which their activity was performed.

The observation that even low-intensity physical activity was associated with lower glucose levels in our participants is consistent with other cross-sectional data which demonstrate that the greatest difference in glucose levels in normal weight older adults (85) and viscerally obese older adults (84) occurred between those reporting participation in light-intensity physical activity related to daily living and those reporting little or no participation in light-intensity physical activity related to daily living.

Higher levels of HDL-C are frequently observed in physically active individuals (31,32,128,131) relative to physically inactive individuals (31,32,128,131). The association between physical activity and HDL-C levels is most consistent among men, however, because men typically have lower HDL-C levels relative to women, and therefore, their HDL-C levels have more room to rise with physical activity. Some cross-sectional studies report a dose-response relationship between increasing levels of physical activity and increasing levels of HDL-C in women (32,128), and some training studies have identified that low- to moderate-intensity physical activity can raise HDL-C levels similar to vigorous-intensity physical activity when controlling for energy expenditure (29,45,60). In the present study, a marginally significant association was observed between HDL-C levels and LTPA. After adjusting for the covariates, mean levels of HDL-C were observed to be somewhat higher in women participating in all intensities of LTPA relative to inactive women, but the standard deviations were too large for the overall trend between HDL-C levels and LTPA to be significant.

The absence of an overall significant association between HDL-C levels and LTPA after adjusting for the covariates in this study has been previously observed in

premenopausal women (12,68,116,128,137) and postmenopausal women using HRT (66,110). For instance, physical activity was not associated with higher HDL-C levels in premenopausal runners using oral contraceptives (128), in premenopausal women using oral contraceptives following ten weeks of aerobic exercise training (137), in premenopausal women using and not using oral contraceptives following four months of aerobic exercise training (116), nor in premenopausal women not using oral contraceptives following ten weeks of aerobic exercise (12). Moreover, a meta-analysis examining the effects of physical activity on HDL-C levels in premenopausal women found no significant increases in HDL-C when compiling data from 27 exercise training studies (68). Lindheim et al. (66) observed no differences in HDL-C levels between postmenopausal women receiving HRT and postmenopausal women receiving HRT with exercise intervention, such that physical activity offered no additional benefit in raising HDL-C levels above that achieved with HRT alone. Furthermore, no significant increases in HDL-C levels were observed following a one-year exercise training study in postmenopausal women exercisers using and not using HRT (110).

The lack of a significant physical activity–related increase in HDL-C levels among premenopausal women and postmenopausal women using HRT may be attributed to the strong influence that premenopausal endogenous estrogen and postmenopausal HRT have on raising HDL-C levels (15,52,136), which limits the extent by which HDL-C levels can rise with physical activity. In our study, 40% of the participants were premenopausal and 74% of the postmenopausal participants were using HRT. Because endogenous estrogen declines following menopause, physical activity may be most effective in raising HDL-C levels in postmenopausal women not using HRT (60,128). In fact, physical activity may attenuate, and perhaps eliminate, the reductions in HDL-C levels that frequently occur after menopause (46). However, only 25% of the postmenopausal women in the present sample (n=19) were not using HRT. Therefore, we lacked power to determine whether physical activity and HDL-C levels were related in postmenopausal women not using HRT. Still, Klebanoff et al. (62) found no significant increases in HDL-C levels in response to 12 weeks of exercise training in either postmenopausal women using HRT or postmenopausal women not using HRT.

The intensity of home and work activity over the previous year was not associated with any of the selected CHD risk factors. Because the physical activity questionnaire used in the present study was based on recall, and because leisure-time forms of physical activity may be more easily recalled than activities such as housework, the inability to find a significant relationship between home activity and reductions in CHD risk may reflect the imprecision or inaccuracy of classification into home activities based on self-report. Furthermore, many of the participants who engaged in moderate to heavy forms of LTPA reported little or no home-related forms of physical activity. The majority of work activity engaged in by employed participants (42%) fell primarily into the intensity categories of inactive and light, which may explain the absence of significant linear associations between work activity and the CHD risk factors.

Another question addressed in the current study was whether the addition of either total body fat, waist circumference (as a measure of abdominal fat accumulation), or dietary intake of fat in the multivariate models would attenuate or eliminate the significant association between LTPA and the metabolic CHD risk factors. Although BMI is most frequently used as a measure of adiposity (97,128,136), BMI is limited in its ability to accurately represent levels of adiposity because it does not distinguish between excess weight for height from fat mass and excess weight for height from fat free mass. Thus, total body fat was used as the measure of adiposity in the regression models.

The rationale for including total body fat and abdominal fat measurements in the multivariate models is based on research which suggests that favorable levels of the metabolic CHD risk factors observed in physically active persons are mediated largely by less total body and abdominal fat accumulation also observed in physically active persons (27,29,132,133,134). By contrast, some evidence suggests that physical activity–related improvements in the metabolic CHD risk factors are primarily mediated by physical activity–induced increases in lipoprotein lipase activity that may occur independently from total body and abdominal fat loss (59,67,126). Our data support the operation of both pathways in that the significant association between LTPA and levels of TG and glucose was attenuated when adding total body fat in the multivariate model,

but significant trends and overall statistical significance was maintained. This suggests that lower levels of total body fat observed in physically active women with MS are partly, but not entirely, responsible for the lower levels of TG and glucose also observed in physically active women with MS.

When including waist circumference into the multivariate models, however, the significant association between LTPA and levels of TG was lost, and the significant association between LTPA and levels of glucose was marginally maintained. These findings suggest that abdominal fat acts as a stronger biological modulator in the causal pathway between physical activity and levels of TG and glucose than body fat, and therefore, explains more of the association between physical activity and levels of TG and glucose than body fat. The greater attenuation, and even loss of statistical significance when waist circumference is added into the multivariate model, emphasizes the importance of maintaining and preventing age- and physical inactivity–related increases in abdominal fat accumulation.

Although body fat and abdominal fat may act as biological mechanisms in the association between the metabolic CHD risk factors and physical activity, dietary intake of fat may act as a confounder in this association. Significant associations between LTPA and levels of TG and glucose were maintained after including dietary intake of fat into the multivariate model, which supports the independent influence that physical activity has on the metabolic CHD risk factors.

In summary, the results from this study show that exercise levels attainable by women with MS were associated with more favorable levels of adiposity and more favorable levels of some of the metabolic CHD risk factors, including lower levels of TG and glucose, and perhaps to some extent, higher levels of HDL-C. Current physical activity recommendations emphasize frequent participation in moderate-intensity physical activity accumulating at least 30 minutes each day. The underlying rationale for the current physical activity recommendations is based on research which suggests that frequent bouts of low- to moderate-intensity physical activity can lower CHD risk similar to a single, longer bout of high-intensity physical activity (2,30,29,54,73,123). Our findings lend support to the current physical activity recommendations by demonstrating that most of the benefit associated with physical activity was accounted

for by comparing the most inactive women with MS to those who participated in light- to moderate-intensity LTPA. The observation that even low-intensity LTPA was significantly associated with lower CHD risk is particularly encouraging for women with MS, who may not be able to realistically participate in high-intensity physical activity due to the limitations imposed by their disability.

SUMMARY

Several studies have shown that the sensory and motor impairments of MS, including fatigue, weakness, ataxia, spasticity, heat intolerance, balance problems, blurred vision, pain, and loss of bladder and bowel control, can profoundly interfere with and limit the extent by which many women with MS can effectively and consistently incorporate health promotion practices into their daily lives (113,114,115). Because health behaviors, including physical activity and dietary habits, can influence the risk for CHD by their association with total body and abdominal fat accumulation, insulin sensitivity, and levels of lipids and lipoproteins, the aim of the first manuscript was to examine CHD risk in women with MS by comparing the frequency of inactivity and the frequency of anthropometric, dietary, and metabolic CHD risk factors between the present sample of women with MS and the general population of women participating in the BRFSS, NHIS, and NHANES III.

Because physical activity practices are reported to be low in women with MS (76,80,90,119), it was originally hypothesized that the majority of the women with MS volunteering for this study would be physically inactive, yet 65% of the participants met the LTPA recommendations described in the 1996 BRFSS by regular participation in light- to moderate-intensity LTPA accumulating at least 30 minutes on at least five days of the week. The most frequently reported activities were gardening, leisurely walking, and stretching. Some women (10.6%) regularly participated in 20 minutes of vigorous-intensity LTPA on at least three days of the week. Because the majority of participants were ambulatory (85.4%) and because more active and health-conscious women are more likely to volunteer for a health behavior study such as this, the large proportion of women reporting LTPA in this study is probably not representative of the total population of women with MS. Still, the high prevalence of physically active behaviors among our participants provides promising evidence that women with MS can remain physically active "within the context of their disability (114)."

Despite the high participation in LTPA, women with MS in this sample were at similar CHD risk as the general population of women without MS with respect to body composition and levels of TG and HDL-C. Although more active women with MS

adopted better dietary habits, including less dietary intakes of total and saturated fat, and higher dietary intakes of fruits and vegetables, 69% of participants exceeded the recommended intakes of dietary fat, and slightly less than half met current dietary recommendations for daily fruit and vegetable intake. It is possible that the high consumption of total fat and low consumption of fruits and vegetables among the majority of study participants may have interfered with some of the positive effects that physical activity had on improving CHD risk, and may be partly responsible for the frequency of the anthropometric and metabolic CHD risk factors observed in this sample. Postmenopausal women using HRT and premenopausal women using oral contraceptives, however, did have more favorable metabolic CHD risk factor profiles relative to postmenopausal and premenopausal women not using hormones.

Because physical activity is known to substantially reduce CHD risk by its association with less total body and abdominal fat accumulation, lower levels of TG, higher levels of HDL-C, and improved insulin sensitivity, the aim of the second manuscript was to determine what intensity of LTPA might be necessary to improve CHD risk in women with MS with respect to the anthropometric and metabolic CHD risk factors. Findings from the second manuscript show that all intensities of LTPA (light, moderate, and heavy) were significantly associated with reduced CHD risk in women with MS. Significantly less total body and abdominal fat accumulation, significantly lower levels of TG and glucose, and marginally higher levels of HDL-C were observed in women with MS reporting participation in light- to moderate-intensity LTPA relative to inactive women with MS. The significant associations between LTPA and abdominal fat accumulation and levels of TG and glucose were maintained after adjusting for several covariates known to influence the CHD risk factors.

Lower amounts of total body and abdominal fat accumulation observed in physically active individuals are suggested to act as biological modulators responsible for the more favorable levels of the metabolic CHD risk factors observed in physically active individuals (27,29,132,133,134). It is often argued that the inclusion of either total body fat or abdominal fat into multiple regression models that attempt to examine the association between physical activity and the metabolic CHD risk factors results in a statistical overcorrection that ultimately underestimates the benefits of physical activity

(42,51). In this study, the significant associations between LTPA and levels of TG and glucose were maintained after including total body fat in the multivariate models, but the significant association between LTPA and TG was lost and the significant association between LTPA and glucose was marginally maintained after including waist circumference in the multivariate models. These results suggest that abdominal fat accumulation is a stronger biological modulator in the causal pathway between physical activity and levels of TG and glucose than total body fat. The observation that more favorable levels of TG and glucose observed in physically active women with MS were mediated in large part through less abdominal fat accumulation also observed in physically active women with MS does not detract from the importance that physical activity has on improving CHD risk. Rather, these findings emphasize the role that physical activity plays in reducing abdominal fat accumulation and ameliorating its associated metabolic and hormonal disturbances.

Current physical activity recommendations, which emphasize at least 30 minutes of moderate-intensity physical activity on most days of the week, are based on research which suggest that low- to moderate-intensity physical activity can lower CHD risk similar to high-intensity physical activity (2,29,30,54,60,73,82,123). The findings from the second manuscript lend support to several studies that have provided the underlying rationale for the current physical activity recommendations by demonstrating that 1.) light- to moderate-intensity LTPA improved CHD risk by its significant associations with less abdominal fat accumulation, lower levels of TG and glucose, and perhaps to some extent, higher levels of HDL-C, and 2.) most of the benefit associated with physical activity was accounted for by comparing the most inactive women with MS to those who reported participation in light- to moderate-intensity LTPA. Thus, low- to moderate-intensity physical activity may be an effective and attainable strategy for reducing CHD risk in women with MS.

It is our hope that physicians will incorporate these findings into their understanding of the importance that *any* physical activity can have on improving health and CHD risk in women with MS. We hope that our findings will help to attenuate some of the perceived barriers that frequently prohibit women with MS from participating in traditional, structured exercise programs, and to convince health care professionals to

include light- to moderate- intensity physical activity prescription into their existing treatment of women with MS. Our results clearly show that even low-intensity physical activity is significantly associated with improved CHD risk and may contribute to important health-related benefits in women with MS. Thus, the present findings are particularly encouraging for women with MS, who may not be able to realistically engage in high-intensity physical activity due to the limitations imposed by their disability.

BIBLIOGRAPHY

1. Alter, M. and M. Yamour. Multiple sclerosis prevalence and nutritional factors. *Transactions of the American Neurological Association* 98:253-254, 1973.

2. Andersen, R.E., R.A. Wadden, S.J. Bartlett, B. Zemel, T.J. Verde, and S.C. Franckowiak. Effects of lifestyle activity vs structured aerobic exercise in obese women. *JAMA* 281:335-340, 1999.

3. Anderson, D.W., J.H. Ellenberg, C.M. Leventhal, S.C. Reingold, M. Rodriguez, and D.H. Silberberg. Revised estimate of the prevalence of multiple sclerosis in the United States. *Annals of Neurology* 31(3):333-336, 1992.

4. Angelopoulos, T.J., R.J. Robertson, F.L. Gross, K.F. Metz, and R.E. Laporte. Effect of repeated exercise bouts on high density lipoprotein-cholesterol and its subfractions HDL_2-C and HDL_3-C. *International Journal of Sports Medicine* 14:196-201, 1993.

5. Astrup, A. Physical activity and weight gain and fat distribution changes with menopause: current evidence and research issues. *Medicine and Science in Sports and Exercise* 31:S497-S661, 1999.

6. Beard, C.M., R.J. Barnard, D.C. Robbins, J.M. Ordovas, and E. Schaefer. Effects of diet and exercise on qualitative and quantitative measures of LDL and its susceptibility to oxidation. *Arteriosclerosis and Thrombosis, and Vascular Biology* 16:201-207, 1996.

7. Bjorntorp, P. The regulation of adipose tissue distribution in humans. *International Journal of Obesity* 20:291-302, 1996.

8. Block, G., M. Woods, A. Potosky, and C. Clifford. Validation of a self-administered diet history questionnaire using multiple diet records. *Journal of Clinical Epidemiology* 43:1327-1335, 1990.

9. Bourey, R.E., W.M. Kohrt, J.P. Kirwan, M.A. Staten, D.S. King, and J.O. Holloszy. Relationship between glucose tolerance and glucose-stimulated insulin response in 65-year-olds. *Journal of Gerontology* 48:M122-M127, 1993.

10. Brewer, H.B., R.E. Greg, J.M. Hoeg, and S.S. Fojo. Apolipoproteins and lipoproteins in human plasma: an overview. *Clinical Chemistry* 34(8):(suppl B), B4-B8, 1988.

11. Brooks, G.A., T.D. Fahey, and T.P. White. *Exercise Physiology: Human Bioenergetics and Its Applications.* Mountain View, CA: Mayfield Publishing Company, 1996.

12. Brownell, K.D., P.S. Bachorik, and R.S. Ayerle. Changes in plasma lipid and lipoprotein levels in men and women after a program of moderate exercise. *Circulation* 65:477-484, 1982.

13. Caprio, S., L.D. Hyman, S. McCarthy, R. Lange, M. Bronson, and W.V. Tamborlane. Fat distribution and cardiovascular risk factors in obese adolescent girls: importance of the intraabdominal fat depot. *American Journal of Clinical Nutrition* 64:12-17, 1996.

14. Carmer, S.G. and M.B. Swanson. An evaluation of ten pairwise multiple comparison procedures by Monte Carlo Methods. *Journal of the American Statistical Association* 68:66-74, 1973.

15. Castelli, W.P. Cardiovascular disease in women. *American Journal of Obstetrics and Gynecology* 158:1553-1560, 1988.

16. Cefalu, W.T., Z.Q. Wang, S. Werbel, et al. Contribution of visceral fat mass to the insulin resistance of aging. *Metabolism* 44:954-959, 1995.

17. Cefalu, W.T., S. Werbel, A.D. Bell-Farrow, et al. Insulin resistance and fat patterning with aging: relationship to metabolic risk factors for cardiovascular disease. *Metabolism* 47:401-408, 1998.

18. Crawford, M.A., P. Budowski, and A. Hassam. Dietary management in multiple sclerosis. *Proceedings of the Nutrition Society* 38:373-389, 1979.

19. Crouse, S.F., B.C. O'Brien, J.J. Rohack, et al. Changes in serum lipids and apolipoproteins after exercise in men with high cholesterol: influence of intensity. *Journal of Applied Physiology* 79:279-286, 1995.

20. Deslypere, J.P. and G. Jackson. A lipid hypothesis: prediction, observation and the triglyceride/HDL gap. *Current Medical Research and Opinion* 14(2):65-78, 1998.

21. Despres, J.P. Visceral obesity, insulin resistance, and dyslipidemia: contribution of endurance exercise training to the treatment of the plurimetabolic syndrome. *Exercise and Sport Science Reviews* 25:271-300, 1997.

22. Despres, J.P., M. Ferlund, S. Moorjani, et al. Role of hepatic-triglyceride lipase activity in the association between intra-abdominal fat and plasma HDL cholesterol in obese women. *Arteriosclerosis* 9:485-492, 1989.

23. Despres, J.P., B. Lamarche, P. Mauriege, et al. Hyperinsulinemia as an independent risk factor for ischemic heart disease. *The New England Journal of Medicine* 334:952-957, 1996.

24. Despres, J.P., S. Lemieux, B. Lamarche, et al. The insulin resistance-dyslipidemic syndrome: contribution of visceral obesity and therapeutic implications. *International Journal of Obesity* 19:S76-S86, 1995.

25. Despres, J.P., S. Moorjan, M. Ferland, et al. Adipose tissue distribution and plasma lipoprotein levels in obese women: Importance of intra-abdominal fat. *Arteriosclerosis* 9:203-210, 1989.

26. Despres, J.P., S. Moorjani, P.J. Lupien, A. Tremblay, A. Nadeau, and C. Bouchard. Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease. *Arteriosclerosis* 10:497-511, 1990.

27. Despres, J.P., M.C. Pouliot, S. Moorjani, et al. Loss of abdominal fat and metabolic response to exercise training in obese women. *American Journal of Physiology* 261:E159-E167, 1991.

28. DiPietro, L., C. Caspersen, A. Ostfeld, and E. Nadel. A survey for assessing physical activity among older adults. *Medicine and Science in Sports & Exercise* 28(5):596-600, 1996.

29. Duncan, J. J., N.F. Gordon, and C.B. Scott. Women walking for health and fitness: how much is enough? *JAMA* 266:3295-3299, 1991.

30. Dunn, A.L., B.H. Marcus, J.B. Kampert, M.E. Garcia, H.W. Kohl, and S.N. Blair. Comparison of lifestyle and structured interventions to increase physical activity and cardiorespiratory fitness. *JAMA* 281:327-334, 1999.

31. Durstine, J. L. and W.L. Haskell. Effects of exercise training on plasma lipids and lipoproteins. *Exercise and Sport Sciences Reviews* 22:477-521, 1994.

32. Durstine, J.L., R.R. Pate, P.B. Sparling, G.E. Wilson, M.D. Senn, and W.P. Bartoli. Lipid, lipoprotein, and iron status of elite women distance runners. *International Journal of Sports Medicine* 8:119-123, 1987.

33. Dworkin, R., D. Bates, J. Millar, and D. Paty. Linoleic acid and multiple sclerosis: a reanalysis of three double-blind trials. *Neurology* 34:1441-1445, 1984.

34. Ebisu, T. Splitting the distance of endurance running: on cardiovascular endurance and blood lipids. *Japanese Journal of Physical Education* 30:37-43, 1985.

35. Evans, D.J., R.G. Hoffmann, R.K. Kalkhoff, and A.H. Kissebah. Relationship of body fat topography to insulin sensitivity and metabolic profiles in premenopausal women. *Metabolism* 33:68-75, 1984.

36. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Summary of the Second Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *JAMA* 269:3015-3023, 1993.

37. Feldman, E.B. Nutrition and diet in the management of hyperlipidemia and atherosclerosis. In Shils, M.E., J.A. Olson, M. Shike (eds): *Modern nutrition in health and disease*. Philadelphia:Lea & Febiger, 1298-1316, 1994.

38. Flegal, K.M., M.D. Carroll, R.J. Kuczmarski, and C.L. Johnson. Overweight and obesity in the United States: prevalence and trends, 1960-1994. *International Journal of Obesity*. 22:39-47, 1998.

39. Fletcher, G.F. How to implement physical activity in primary and secondary prevention. *Circulation* 96:355-357, 1997.

40. Friedwald, W.T., R.I. Levy, and D.S. Fredrickson. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without the use of the preparative ultracentrifuge. *Clinical Chemistry* 18:499-502, 1972.

41. Ginsberg, H.N. Lipoprotein physiology in nondiabetic and diabetic states: relationship to atherogenesis. *Diabetes Care* 14:839-855, 1991.

42. Greendale, G.A., L. Bodin-Dunn, S. Ingles, R. Haile, and E. Barrett-Connor. Leisure, home, and occupational physical activity and cardiovascular risk factors in postmenopausal women. *Archives of Internal Medicine* 156:418-424, 1996.

43. Groff, J.L., S.S. Gropper, and S.M. Hust. *Advanced Nutrition and Human Metabolism.* St. Paul, MN: West Publishing Company, 1995.

44. Han, D.H., P.A. Hansen, H.H. Host, and J.O. Holloszy. Insulin resistance of muscle glucose transport in rats fed a high-fat diet. *Diabetes* 46:1761-1767, 1997.

45. Hardman, A.E. Physical activity, obesity and blood lipids. *International Journal of Obesity* 23:S64-S71, 1999.

46. Harting, G.H., C.E. Moore, R. Mitchell, and C.M. Kappus. Relationship of menopausal status and exercise level to HDL cholesterol in women. *Experimental Aging Research* 10:13-18, 1984.

47. Haskell, W.L. Health consequences of physical activity: understanding and challenges regarding dose-response. *Medicine and Science in Sports and Exercise* 26:649-660, 1994.

48. Herbert, P.N., D.N. Bernier, E.M. Cullinane, L. Edelstein, M.A. Kantor, and P.D. Thompson. High-density lipoprotein metabolism in runners and sedentary men. *JAMA* 252(8):1034-1037, 1984.

49. Heyward, V.H. and L.M. Stolarczyk. *Applied Body Composition Assessment.* Champaign, FL: Human Kinetics, 1996.

50. Host, H.H., P.A. Hansen, L.A. Nolte, M.M. Chen, and J.O.Holloszy. Rapid reversal of adaptive increases in muscle GLUT-4 and glucose transport capacity after training cessation. *Journal of Applied Physiology* 84(3):798-802, 1998.

51. Hu, F.B., R.J. Sigal, J.W. Rich-Edwards, et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women. *JAMA* 282:1433-1439, 1999.

52. Hulley, S., D. Grady, T. Bush, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *JAMA* 280:605-613, 1998.

53. Hurley, B.F. and J.M. Hagberg. Optimizing health in older persons: aerobic or strength training? *Exercise and Sports Science Reviews* 26:61-90, 1998.

54. Jakcic, J.M., C. Winters, W. Lang, and R.R. Wing. Effects of intermittent exercise and use of home exercise equipment on adherence, weight loss, and fitness in overweight women. *JAMA* 282:1554-1560, 1999.

55. Kannel, W.B. and D.L. McGee. Diabetes and glucose tolerance as risk factors for cardiovascular disease: the Framingham Study. *Diabetes Care* 2:120-126, 1979.

56. Kantor, M.A., E.M. Cullinane, S.P. Sady, P.N. Herbert, and P.D. Thompson. Exercise acutely increases high density lipoprotein-cholesterol and lipoprotein lipase activity in trained and untrained men. *Metabolism* 36(2):188-192, 1987.

57. Karjalainen, L., J. Pihlajamaki, P. Karhapaa, and M. Laakso. Impaired insulin-stimulated glucose oxidation and free fatty acid suppression in patients with familial combined hyperlipidemia: a precursor defect for dyslipidemia? *Arteriosclerosis and Thrombosis, and Vascular Biology* 18:1548-1553, 1998.

58. Kent-Braun, J., A. Ng, M. Castro, et al. Strength, skeletal muscle composition, and enzyme activity in multiple sclerosis. *Journal of Applied Physiology* 83(6):1998-2004, 1997.

59. Kiens, B. and H. Lithell. Lipoprotein metabolism influenced by training-induced changes in human skeletal muscle. *Journal of Clinical Investigation* 83:558-564, 1989.

60. King, A.C., W.L. Haskell, D.R. Young, R.K. Oka, and M.L. Stefanick. Long-term effects of varying intensities and formats of physical activity on participation rates, fitness, and lipoproteins in men and women aged 50 to 65 years. *Circulation* 91:2596-2604, 1995.

61. Kirwan, J.P., W.M. Kohrt, D.M. Wojita, R.E. Bourey, and J.O. Holloszy. Endurance exercise training reduces glucose-stimulated insulin levels in 60- to 70-year-old men and women. *Journal of Gerontology* 48:M84-M90, 1993.

62. Klebanoff, R., V.T. Miller, and B. Fernhall. Effects of exercise and estrogen therapy on lipid profiles of postmenopausal women. *Medicine and Science in Sports and Exercise* 30:1028-1034, 1998.

63. Kohrt, W.M., J.P. Kirwan, M.S. Staten, R.E. Bourey, D.S. King, and J.O. Holloszy. Insulin resistance in aging is related to abdominal obesity. *Diabetes* 42:273-281, 1993.

64. Kraft, G.H., J.E. Freal, and J.K. Coryell. Disability, disease duration, and rehabilitation service needs in multiple sclerosis: patient perspectives. *Archives of Physical Medicine and Rehabilitation* 67:164-168, 1986.

65. Lemieux, S., D. Prud'homme, A. Nadeau, A. Tremblay, C. Bouchard, and J.P. Despres. Seven-year changes in body fat and visceral adipose tissue in women: Associations with indexes of plasma glucose-insulin homeostasis. *Diabetes Care* 19:983-991, 1996.

66. Lindheim, S.R., M.Notelovitz, E.B. Feldman, S.Larsen, F.Y. Khan, and R.A. Lobo. The independent effects of exercise and estrogen on lipids and lipoproteins in postmenopausal women. *Obstetrics and Gynecology* 83:167-172, 1994.

67. Lithell, H., M. Cedermark, J. Froberg, P. Tesch, and J. Karlsson. Increase of lipoprotein-lipase activity in skeletal muscle during heavy exercise. Relation to epinephrine excretion. *Metabolism* 30(11):1130-1134, 1981.

68. Lokey, E.A. and Z.V. Tran. Effects of exercise training on serum lipid and lipoprotein concentrations in women: a meta-analysis. *International Journal of Sports Medicine* 10:424-429, 1989

69. Mayer-Davis, E., R. D'Agostino, A. Karter, et al. Intensity and amount of physical activity in relation to insulin sensitivity. *JAMA* 279:669-674, 1998.

70. McArdle, WD., F.L. Katch, and V.L. Katch. *Exercise Physiology: Energy, Nutrition, and Human Performance.* Baltimore, MD: Williams & Wilkins, 1996.

71. McMurry, M., W.Connor, D. Lin, M. Cerqueira, and S. Connor. The absorption of cholesterol and the sterol balance in the Tarahumara Indians of Mexico fed cholesterol-free and high cholesterol diets. *American Journal of Clinical Nutrition* 41:1289-1298, 1985.

72. Miller Bass, K., C.J. Newschatter, M.J. Klag, and T.L. Bush. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Archives of Internal Medicine* 153:2209-2216, 1993.

73. Murphy, M.H. and A.E. Hardman. Training effects of short and long bouts of brisk walking in sedentary women. *Medicine and Science in Sports and Exercise* 30, 152-157, 1998.

74. Navarro, X. and R. Segura. Plasma lipids and their fatty acid composition in multiple sclerosis. *Acta Neurological Scandinavica* 78:152-157, 1988.

75. Newcombe, J., H. Li, and M.L. Cuzner. Low density lipoprotein uptake by macrophages in multiple sclerosis plaques: implications for pathogenesis. *Neuropathology and Applied Neurobiology* 20:152-162, 1994.

76. Ng, A.V. and J. Kent-Braun. Quantification of lower physical activity in persons with multiple sclerosis. *Medicine and Science in Sports &Exercise* 29(4):517-523, 1997.

77. Nikkila, E.A. HDL in relation to the metabolism of triglyceride-rich lipoproteins. In Miller, N.E and G.J. Miller (eds): *Clinical and Metabolic Aspects of High-Density Lipoproteins*. Amsterdam:Elsevier Science Publishers BV, 217-245, 1984.

78. Nikkila, E.S., M.R. Taskinen, S. Rehunen, and M. Harkonen. Lipoprotein lipase activity in adipose tissue and skeletal muscle of runners: relation to serum lipoproteins. *Metabolism* 27:1661-1671, 1978.

79. Oakes, N.D., K.S. Bell, S.M. Furler, et al. Diet-induced muscle insulin resistance in rats is ameliorated by acute dietary lipid withdrawal or a single bout of exercise: Parallel relationship between insulin stimulation of glucose uptake and suppression of long-chain fatty acyl-CoA. *Diabetes* 46:2022-2028, 1997.

80. Olgiati, R., J. Jacquet, and P. Di Prampero. Energy cost of walking and exertional dyspnea in multiple sclerosis. *American Review of Respiratory Disease* 134:1005-1010, 1986.

81. Owens, J.F., K.A. Matthews, R.R. Wing, and L.H. Kuller. Physical activity and cardiovascular risk: a cross-sectional study of middle-aged premenopausal women. *Preventive Medicine* 19:147-157, 1990.

82. Pate, R.R., M. Pratt, S.N. Blair, et al. Physical activity and public health: a recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *JAMA* 273:402-407, 1995.

83. Peltonen, P., J. Marniemi, E. Hietanen, I. Vuori, and C. Ehnholm. Changes in serum lipids, lipoproteins, and heparin releasable lipolytic enzymes during moderate physical training in man: a longitudinal study. *Metabolism* 30(5):518-526, 1981.

84. Pescatello, L.S. and D. Murphy. Lower intensity physical activity is advantageous for fat distribution and blood glucose among viscerally obese older adults. *Medicine and Science in Sports and Exercise* 30:1408-1413, 1998.

85. Pescatello, L.S., D. Murphy, and L.DiPietro. Daily movement, adiposity, and blood glucose among older adults of middle to lower socioeconomic status. *American Journal of Public Health* 86:592-593, 1996.

86. Petajan, J.H., E. Gappmaier, A. White, et al. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Annals of Neurology* 39:432-441, 1996.

87. Petajan, J.H. and A.T. White. Recommendations for physical activity in persons with multiple sclerosis. *Sports Medicine* 27:179-191, 1999.

88. Pi-Sunyer, F.X. Cormorbidities of overweight and obesity: current evidence and research issues. *Medicine and Science in Sports and Exercise* 31:S602-S608, 1999

89. Ponichtera-Mulcare, J.A. Exercise and multiple sclerosis. *Medicine and Science in Sports & Exercise* 25(4):451-465, 1993.

90. Ponichtera-Mulcare, J.A., R.M. Glaser, T. Mathews, and D.N. Camaione. Maximal aerobic exercise in persons with multiple sclerosis. *Clinical Kinesiology* Winter:12-21, 1993.

91. Pouliot, M.C., J.P. Despres, S. Lemieux, et al. Waist circumference and abdominal sagittal diameter: and related cardiovascular risk in men and women. *American Journal of Cardiology* 73:460-468, 1994.

92. Pouliot, M.C., J.P. Despres, A. Nadeau, et al. Visceral obesity in men: associations with glucose tolerance, plasma insulin, and lipoprotein levels. *Diabetes* 41:826-834, 1992.

93. Pratt, M., C.A. Macero, and C. Blanton. Levels of physical activity and inactivity in children and adults in the United States: current evidence and research issues. *Medicine and Science in Sports and Exercise.* 31:S526-S533, 1999.

94. Pyorala, M., H. Miettinen, M. Laakso, and K. Pyorala. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: the 22-year follow-up results of the Helsinki policemen study. *Circulation* 98:398-404, 1998.

95. Randle, P.J., P.B. Garland, C.N. Hales, and E.A. Newsholme. The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet* 1:785-789, 1963.

96. Reaven, B. Role of insulin resistance in human disease. *Diabetes* 37:1595-1607, 1988.

97. Reaven, P.D., J. B. McPhillips, E.L. Barrett-Connor, and M.H. Criqui. Leisure time exercise and lipid and lipoprotein levels in an older population. *Journal of the American Geriatrics Society* 38:847-854, 1990.

98. Reaven, G.M. Pathophysiology of insulin resistance in human disease. *Physiological Sciences* 75(3):473-486, 1995.

99. Ren, J.M., C.F. Semenkovich, E.A. Gulve, J. Gao, and J.O. Holloszy. Exercise induces rapid increases in GLUT 4 expression, glucose transport capacity, and insulin-stimulated glycogen storage in muscle. *The Journal of Biological Chemistry* 269:14396-14401, 1994.

100. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183-1197, 1997.

101. Rexrode, K.M., V.J. Carey, C.H. Hennekens, et al. Abdominal adiposity and coronary heart disease in women. *JAMA* 280:1843-1848, 1998.

102. Rimmer, J.H. *Fitness and Rehabilitation Programs for Special Populations.* Dubuque, IA: Brown & Benchmark, 1994.

103. Rosner, L.J. and S.Ross. *Multiple Sclerosis.* New York, NY:Simons and Schuster, 1992.

104. Sadovnick, A.D., K. Eisen, B.C. Ebers, and D.W. Paty. Cause of death in patients attending multiple sclerosis clinics. *Neurology* 41:1193-1196, 1991.

105. Sady, S.P., P.D. Thompson, E.M. Cullinane, M.A. Kantor, E. Domagala, and P.N. Herbert. Prolonged exercise augments plasma triglyceride clearance. *JAMA* 256(18):2552-2555, 1986.

106. Seidell, J.C., P. Bjorntorp, L. Sjostrom, H. Kvist, and R. Sannerstedt. Visceral fat accumulation in men is positively associated with insulin, glucose, and C-peptide levels, but negatively with testosterone levels. *Metabolism* 39:897-901, 1990.

107. Seip, R.L., P. Moulin, T. Cocke, A. et al. Exercise training decreases plasma cholesteryl ester transfer protein. *Arteriosclerosis and Thrombosis* 13:1359-1367, 1993.

108. Shapiro, R.T., J. Petajan, D. Kosich, B. Molk, and J. Feeney. Role of cardiovascular fitness in multiple sclerosis: a pilot study. *Journal of Neurological Rehabilitation* 2:43-49, 1988.

109. Smith, S.C., S.N. Blair, M.H. Criqui et al. Preventing heart attack and death in patients with coronary disease. *Circulation* 92:2-4, 1995.

110. Stefanick, M.L., S. Mackey, M. Sheehan, N. Ellsworth, W.L. Haskell, and P.D. Wood. Effects of diet and exercise in men and postmenopausal women with low levels of HDL cholesterol and high levels of LDL cholesterol. *The New England Journal of Medicine* 339;12-20, 1998.

111. Stefanick, M.L., R.B. Terry, W.L. Haskell, and P.D. Wood. Relationships of changes in post-heparin hepatic and lipoprotein lipase activity to HDL-cholesterol changes following weight loss achieved by dieting versus exercise. In Gallo, L. (ed): *Cardiovascular Disease: Molecular and Cellular Mechanisms, Prevention, and Treatment.* Plenum Press, 61-68, 1987.

112. Stein, R.A., D.W. Michiella, M.D. Glantz, H. Sardy, and A. Cohen. Effects of different exercise training intensities on lipoprotein cholesterol fractions in healthy middle-aged men. *American Heart Journal* 119(2):277-283, 1990.

113. Stuifbergen, A.K. Health-promoting behaviors and quality of life among individuals with multiple sclerosis. *Scholarly Inquiry for Nursing Practice: An International Journal* 9(1):31-50, 1995.

114. Stuifbergen, A.K. and G.J. Roberts. Health promotion practices of women with multiple sclerosis. *Archives of Physical Medicine and Rehabilitation* 78 (12 Suppl 5):S3-S9, 1997.

115. Stuifbergen, A.K. and S. Rogers. Persons with chronic disabling conditions. *Advances in Nursing Science* 19(4):1-20, 1997.

116. Suter, E. and B. Marti. Little effect of long-term, self-monitored exercise on serum lipid levels in middle-aged women. *Journal of Sports Medicine and Physical Fitness* 32:400-411, 1992.

117. Swank, R.L. Multiple Sclerosis: fat-oil relationship. *Nutrition* 7:368-376, 1991.

118. Tall, A. R. Plasma high-density lipoproteins: metabolism and relationship to atherogenesis. *The Journal of Clinical Investigations* 86:379-384, 1990.

119. Tantucci, C., M. Massucci, R. Piperno, V. Grassi, and C. Sorbini. Energy cost of exercise in multiple sclerosis patients with low degree of disability. *Multiple Sclerosis* 2(3):161-167, 1996.

120. Thompson, P.D., S. Yurgalevitch, M.F. Flynn, et al. Weight loss is not required to increase HDL-C with exercise training. *Circulation* 86(Suppl I):I-590, 1992.

121. Thompson, R.H. Fatty acid metabolism in multiple sclerosis. *Biochemical Societal Symposia* 35:103-111, 1973.

122. Tikkanen, M.J. and E.A. Nikkila. Regulation of hepatic lipase and serum lipoproteins by sex steroids. *American Heart Journal* 113:565-567, 1987.

123. U.S. Department of Health and Human Services. *Physical Activity and Health: A Report of the Surgeon General.* Atlanta Georgia: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, 1996.

124. Wallberg-Henriksson, H., J. Rincon, and J.R. Zierath. Exercise in the management of non-insulin-dependent diabetes mellitus. *Sports Medicine* 25:25-35, 1998.

125. Warnick, R.G. and E. Teng Leary. Analytical procedures for measurement of the lipids and lipoproteins in cardiovascular risk assessment. In Spille, G.A. (ed): *Handbook of Lipids in Human Nutrition.* Boca Raton FL:CRC Press, Inc., 21-28, 1996.

126. Weintraub, M.S., Y. Rosen, R. Otto, S. Eisenberg, and J.L. Breslow. Physical exercise conditioning in the absence of weight loss reduces fasting and postprandial triglyceride-rich lipoprotein levels. *Circulation* 79:1007-1014, 1989.

127. Williams, D.P., S.B. Going, T.G. Lohman, M.J. Hewitt, and A.E. Haber. Estimation of body fat from skinfold thicknesses in middle-aged and older men and women: a multiple component approach. *American Journal of Human Biology* 4:595-605, 1992.

128. Williams, P. T. High-density lipoprotein cholesterol and other risk factors for coronary heart disease in female runners. *The New England Journal of Medicine* 334:1298-1303, 1996.

129. Williams, P. T., R.M. Krauss, M.L. Stefanick, K.M. Vranizan, and P.D. Wood. Effects of low-fat diet, calorie restriction, and running on lipoprotein subfraction concentration in moderately overweight men. *Metabolism* 43:655-663, 1994.

130. Williams, P.T., R.M. Krauss, K.M. Vranizan, and P.D. Wood. Changes in lipoprotein subfractions during diet-induced and exercise-induced weight loss in moderately oerweight men. *Circulation* 81:1293-1304, 1990.

131. Wood, P. D., W. Haskell, H. Klien, S. Lewis, M.P. Stern, and J.W. Farquhar. The distribution of plasma lipoproteins in middle-aged male runners. *Metabolism* 25(11):1249-1256, 1976.

132. Wood, P.D. W.L. Haskell, S.N. Blair, P.T., et al. Increased exercise level and plasma lipoprotein concentrations: a one-year, randomized, controlled study in sedentary, middle-aged men. *Metabolism* 32:31-39, 1983.

133. Wood, P.D., M.L. Stefanick, D.M. Dreon, et al. Changes in plasma lipid and lipoproteins in overweight men during weight loss through dieting as compared with exercise. *The New England Journal of Medicine* 319:1173-1179, 1988.

134. Wood, P.D., M.L. Stefanick, P.T. Williams, and W.L. Haskell. The effects on plasma lipoproteins of a prudent weight-reducing diet, with or without exercise, in overweight men and women. *The New England Journal of Medicine* 325:361-466, 1991.

135. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity. Geneva: World Health Organization, 1998.

136. Writing Group for the PEPI Trial. Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. *JAMA* 273:199-208, 1995.

137. Wynne, T., M.A. Frey, L.L. Laubach, C.J. Glueck. Effect of a controlled exercise program on serum lipoprotein levels in women on oral contraceptives. *Metabolism* 29:1267-1271, 1980.

APPENDICES

APPENDIX A

INSTITUTIONAL REVIEW BOARD PROPOSAL

OSU Institutional Review Board (IRB)

Differences in Coronary Heart Disease Risk Factors between Active and Inactive Women with Multiple Sclerosis

Application for Approval of the OSU Institutional Review Board (IRB)
For the protection of Human Subjects

1. Significance of the Project.

Women are twice as likely to develop multiple sclerosis (MS) than men. The majority of women with MS will live at least 90% of a full life span. However, because women with MS frequently have low participation in physically active behaviors and because physical inactivity is designated as a major coronary heart disease (CHD) risk factor, women with MS may be at increased risk for CHD as they age. In fact, physically inactive individuals are 1.5 to 2.4 times more likely to develop CHD relative to their physically active counterparts.

Physical inactivity raises CHD risk, in part, by its association with abdominal fat gain, high circulating levels of triglycerides (TG), and low circulating levels of high density lipoprotein-cholesterol (HDL-C). High levels of TG and low levels of HDL-C are strong, independent, metabolic predictors of CHD risk in women. Furthermore, age-related reductions in physical activity contribute to age-related gains in abdominal fat, which in turn, is associated with, and may be the initial defect contributing to increases in circulating levels of TG and reductions in circulating levels of HDL-C in women.

The United States Surgeon General emphasizes the need for research focusing on preventative measures for reducing CHD risk, specifically in women and those with disabilities. Because physical activity substantially reduces CHD risk, in large part, by its association with low amounts of abdominal fat, low circulating levels of TG, and high circulating levels of HDL-C, *the primary aim of the proposed study is to determine whether levels of abdominal fat, TG, and HDL-C differ between active and inactive women with MS.* The primary aim is intended to determine whether more active women with MS are at lower CHD risk than less active women with MS. Furthermore, the primary aim may provide valuable information for establishing preliminary physical activity guidelines for reducing CHD risk in women with MS.

2. Methods and Procedures.

The proposed study is a cross-sectional study examining the differences in CHD risk factors between active and inactive women with MS. Data will be collected at the Health and Human Performance Lab at Oregon State University in Corvallis, the Rogue Valley Medical Center in Medford, the Willamalane Senior Center in Springfield, the Salem Rehabilitation Center in Salem, and the Multiple Sclerosis Clinic in Portland.

Data collection from testing sites will require approximately 4 months to complete. Trained undergraduate seniors and graduate students will assist with data collection.

Data collection for each subject will require no more than 2.0 hours to obtain. During the lab visit: 1.) venous blood will be collected for measurement of lipid and lipoprotein-cholesterol levels (total cholesterol (TC), TG, low-density lipoprotein-cholesterol (LDL-C), and HDL-C); 2.) skinfold thicknesses and girth circumferences will be obtained for estimation of total and abdominal body fat; and 3.) information regarding physical activity, dietary habits and composition, and medical history will be obtained by interviewer- and self-administered questionnaires. The data collected from the physical activity, dietary composition, and medical history questionnaires will be used to estimate the extent by which overall health behavior differences may contribute to CHD metabolic risk factors in women with MS.

Blood Collection

Venous blood (<20 millimeters) will be collected by venipuncture following a 12-hour fast by a trained technician using sterile procedures. Firm pressure and a bandage will be applied to the venipuncture site immediately following the blood draw. Approximately 10 to 15 minutes is required to collect the blood samples for each person. Plasma and red blood cells will be separated by centrifugation at 1900 x g for 15 minutes. The plasma will be transferred to plastic labeled vials and frozen at –70C for later analysis of lipid and lipoprotein-cholesterol concentrations.

Assessment of Lipids and Lipoproteins

Lipid and lipoprotein cholesterol levels (TC, TG, LDL-C, and HDL-C) will be measured by Rosemary Wander, Ph.D., in the Lipids Laboratory in the Department of Nutrition and Food Management at Oregon State University. Quality control of Dr. Rosemary Wander's laboratory is monitored by the Lipid Standardization Program of the Centers for Disease Control and Prevention. TC, TG, and HDL-C will be directly measured by enzymatic procedures. LDL-C will be calculated indirectly from the direct measurements of TC, TG, and HDL-C.

Anthropometry for Assessment of Total and Abdominal Body Fat

Body weight will be measured with a standard balance-beam scale in light clothing without shoes. Height will also be measured without shoes using a stadiometer. Total body fat will be calculated from equations using skinfold thicknesses as an estimate of subcutaneous fat. Skinfold thicknesses will be measured with a Lange skinfold caliper at 4 sites on the right side of the body (triceps, subscapular, abdominal, and calf) by a trained lab assistant according to standardized procedures. Because it is undetermined whether more favorable blood levels of TG and HDL-C observed in physically active individuals is independent from lower amounts of total body fat also observed in physically active individuals, the proposed study will determine whether the association

between physical activity and blood levels of TG and HDL-C are independent from total body fat in the study sample of women with MS.

Waist and hip circumferences will be measured with a tape measure. Waist circumference and the waist to hip ratio will be used as an index for abdominal obesity in the data analysis. Recent evidence suggests that the waist circumference may be the most accurate anthropometric measure of abdominal and intra-abdominal obesity. Because abdominal fat gain may proceed the onset of the CHD metabolic risk factors, the proposed study will quantify the association between increasing amounts of abdominal fat and increasing levels of blood TG, and between increasing amounts of abdominal fat and decreasing levels of blood HDL-C in study participants. Approximately 20 minutes is required to obtain the skinfold thicknesses and girth circumferences for assessment of total and abdominal fat.

Physical Activity Assessment

The Yale Physical Activity Survey (YPAS) will be used as an unobtrusive means for assessing physical activity levels of the study participants. Because the YPAS accounts for lower-intensity, home-related activities and other activities related to daily living, the YPAS is the most appropriate measurement tool available for estimating physical activity in women with MS. During the administration of the YPAS, subjects are asked to respond to interviewer-administered questions regarding their participation in common home- and yard-related activities, exercise- and recreational-related activities, and daily living-related activities. The YPAS is a valid and reliable measurement tool requiring 20–30 minutes to administer.

A brief 12-month physical activity questionnaire used in the Postmenopausal Estrogens/Progestins Intervention (PEPI) Study will be administered during the initial eligibility telephone screening interview to assess occupational, home, and leisure-time physical activity over the entire year. The information obtained from the PEPI Physical Activity Questionnaire will stratify the women volunteers into various activity levels prior to actual data collection so that equal representation of moderately physically active women with MS, lightly physically active women with MS, and physically inactive women with MS will be achieved. Administration of the PEPI Physical Activity Questionnaire will take approximately 5 minutes.

Diet Composition

Eating habits and diet composition will be assessed by the self-administered Block Food Frequency Questionnaire. The Block Food Frequency Questionnaire provides valid and reliable information regarding dietary intake of total fat, saturated fat, cholesterol, fiber, and nutritional supplements. Because high saturated fat and cholesterol intake substantially raises CHD risk, and because some evidence suggests that high saturated fat intake is linked with an increase in the frequency and severity of exacerbations, and overall deterioration associated with MS, the inclusion of a dietary analysis is necessary to determine the extent of dietary intake of saturated fat and cholesterol among study

participants. Because antioxidant nutritional supplement use reduces CHD risk, the quantification of dietary intake of supplements is necessary to control for the confounding influence of antioxidant use in the data analysis. Moreover, because low-fat diets are associated with high TG levels and low HDL-C levels, an appropriate dietary analysis is necessary to consider how potential differences in total fat intake among study participants may confound the interpretations regarding the true association between physical activity and circulating levels of TG and HDL-C. The Block Food Frequency Questionnaire requires approximately 30-40 minutes to complete.

Medical History

Because hormone replacement therapy (HRT) use, smoking history, alcohol consumption, and some medications are known to influence the CHD metabolic risk factors, a brief medical history questionnaire will be administered to obtain important information regarding personal habits, previous and current HRT use, and lipid and lipoprotein-cholesterol altering medications of study participants in order to control for such potential confounders in the data analysis. In addition, because health promotion practices frequently decline with increasing disability associated with the complications of MS, the medical history questionnaire will obtain information regarding mobility levels among study participants in order to quantify the association between the metabolic CHD risk factors and the severity of MS. The medical history questionnaire will require approximately 10 minutes to complete.

Data Analysis

Analysis of covariance will be used to determine whether the selected CHD risk factors (abdominal fat, TG, and HDL-C) differ between active and inactive women with MS after adjusting for age, lipid and lipoprotein-cholesterol altering medication use, and HRT use. Logistic regression will be performed to quantify the relationship between the selected CHD risk factors on the log odds of the probability of having severe MS unadjusted and adjusted for age, lipid and lipoprotein-cholesterol altering medication use, and HRT use. To quantify the association between abdominal fat and TG, and between abdominal fat and HDL-C, separate multiple linear regressions will be performed after adjusting for the effects of age, lipid and lipoprotein-cholesterol altering medication use, and HRT use. To determine whether the association between physical activity and circulating levels of TG and HDL-C is independent from total body fat, multivariate linear regression will be performed.

3. Benefits and Risks.

Benefits

Subjects participating in the study will receive information regarding their: 1.) lipid and lipoprotein-cholesterol profile, and current recommendations from the National Cholesterol Education Program and the Lipid Clinics' Follow-up Study to help them

interpret and understand their test results; 2.) dietary intake of total fat, saturated fat, cholesterol, sodium, fiber, and antioxidants, and current recommendations from the American Dietetics Association to help them understand their dietary assessment; 3.) total and abdominal fat measurements, and comparisons to national normative values and to values associated with increased health risks for women; and 4.) total accumulated time spent in physically active behaviors during a typical week, and recommendations from the United States Surgeon General regarding how much physical activity may be necessary to achieve health-related benefits.

Risks

Some discomfort and minor bruising may occur during the blood draw. To minimize discomfort and the risk of infection, sterile procedures during the blood collection will be used by a trained technician, and firm pressure and a bandage will be applied to the venipuncture site following the blood draw.

Minor discomfort may be associated with the skinfold measurements from the pinching of the skin with the skinfold calipers. Discomfort will be minimized by having experienced lab assistants conduct the skinfold measurements according to standardized procedures to reduce the time necessary to achieve accurate measurements.

The physical activity, dietary assessment, and medical history questionnaires may seem tedious. Fatigue related to completing the questionnaires will be minimized by measuring total and abdominal body fat, and providing a snack between administration of questionnaires.

4. Subject Population.

Approximately 100 volunteers for the proposed study will be recruited from Oregon MS chapters, physician referrals, and existing databases developed from previous studies involving women volunteers with MS at Oregon State University who have agreed to be contacted for future studies. Physicians from the Medford Neurological and Spine Clinic and physicians on the Institutional Review Board at Rogue Valley Medical Center have agreed to discuss the proposed study with their MS patients during their office visits. Patients interested in participating in the proposed study will be given Jennifer Slawta's phone number for further information regarding the study. In addition, Jennifer Slawta will present the study at Oregon self-help meetings for recruitment of interested participants. Because MS affects twice as many women than men and because the United States Surgeon General emphasizes the need for research addressing preventative measures for reducing CHD risk in women and persons with disabilities, subjects recruited for the proposed study will be exclusively women with MS. Women with cardiovascular disease, diabetes, or gout, women who currently smoke more than 10 cigarettes per day or consume more than 4 alcoholic beverages per day, and women currently using thyroid, corticosteroid, or gout medications, will not be recruited for participation in the proposed study. Although 95% of the MS population is Caucasian, there are no ethnic restrictions for participation in the proposed study.

Subject recruitment for the proposed study will be aimed to achieve equal representation in each of 3 activity groups as defined by the PEPI Physical Activity Questionnaire including moderately physically active women with MS, lightly physically active women with MS, and physically inactive women with MS. Physically active women volunteers with MS will be recruited from existing databases developed from previous and ongoing MS training studies in the Health and Human Performance Department at Oregon State University. The majority of physically inactive women volunteers with MS will be recruited from the Ashland/Medford area.

5. Informed Consent Document.

A copy of the informed consent for the proposed study is attached.

6. Methods by which the informed consent will be obtained.

Participants will be asked to read and sign the informed consent prior to their participation in the proposed study. Participants will be informed of their right to withdraw from the study at any time without prejudice. Any questions regarding the proposed study, testing procedures, or any other subject concerns, will be answered by the principal investigator or, if appropriate, the research staff.

7. Method by which subject confidentiality will be maintained.

Subject information will only be available to the researcher and research staff of the proposed study. Subject's identity will remain anonymous in the study results by the use of identification numbers instead of names in the data entry and analysis. A data file will be created to link subjects' identity (names, addresses, and phone numbers) with the data in order to send participants their test results and information regarding how to interpret and understand their test results. This link file will only be accessible to the researchers and will not be kept past the project duration. In addition, a separate file will be created only with subjects' names, addresses, and phone numbers exclusively for subjects who agree to be contacted for future studies. This file will be kept beyond the project duration for recruitment of subjects for future related research.

8. Questionnaires, surveys, and testing instruments.

The Yale Physical Activity Survey, the Postmenopausal Estrogens/Progestins Intervention Physical Activity Questionnaire, the Block Food Frequency Questionnaire, and the medical history questionnaire are attached.

9. Other approvals.

Attached is approval granted by the Rogue Valley Medical Center IRB on April 22, 1999.

APPENDIX B

INFORMED CONSENT

OSU Institutional Review Board (IRB)

OREGON STATE UNIVERSITY

Informed Consent Form

A. Title of the Research Project
Differences in Coronary Heart Disease Risk Factors between Active and Inactive Women with Multiple Sclerosis.

B. Investigators
Jeff McCubbin, Ph.D. (principal investigator), Anthony Wilcox, Ph.D. (principal investigator), Jennifer Slawta, M.S. (investigator), Rosemary Wander, Ph.D. (co-investigator).

C. Purpose of the Research Project
Multiple Sclerosis (MS) affects twice as many women than men and coronary heart disease (CHD) is responsible for the majority of deaths in women in the United States. The United States Surgeon General designates physical inactivity as a major CHD risk factor. Because physical activity substantially reduces CHD risk, in large part, by its association with favorable levels of blood cholesterol and low levels of abdominal fat, *the primary aim of the proposed study is to determine whether blood cholesterol levels and abdominal fat differ between active and inactive women with MS.*

We hope to determine whether more active women with MS are at a lower CHD risk than less active women with MS. Furthermore, we hope that the information gathered from this study will help establish minimal physical activity recommendations necessary to reduce CHD risk in women with MS.

D. Procedures
Women with established cardiovascular disease, diabetes, or gout, women who currently smoke more than 10 cigarettes per day or consume more than 4 alcoholic beverages per day, and women currently using thyroid, corticosteroid, or gout medications, will not participate in the proposed study. Data collection for each subject will require approximately 2.0 hours to obtain. During the lab visit:

1.) Blood will be collected from a forearm vein for measurement of blood cholesterol levels following a 12–hour fast.
2.) Body weight and height will be measured in light clothing without shoes. Waist and hip circumferences will be measured with a tape measure for estimation of abdominal fat. Skinfold thicknesses will be measured with a skinfold caliper at 4 sites on the right side of the body (back of the upper arm, below the shoulder blade, abdomen, and calf) for estimation of total body fat. All body fat measurements and recording of body fat measurements will be conducted by trained female technicians.
3.) Information regarding physical activity, eating habits, and medical history will be obtained by interviewer- and self-administered questionnaires. Although the questionnaires may seem tedious, the information gathered

from these questionnaires is necessary to estimate the extent by which overall health behavior and medical history differences may contribute to CHD risk in women with MS.

E. Risks and Discomforts

Some discomfort and minor bruising may occur during the blood draw. To minimize discomfort and the risk of infection, sterile procedures during the blood collection will be used by a trained technician, and firm pressure and a bandage will be applied to the venipuncture site following the blood draw.

Minor discomfort may be associated with the skinfold measurements from the pinching of the skin with the skinfold calipers. Discomfort will be minimized by having experienced lab assistants conduct the skinfold measurements according to standardized procedures to reduce the time necessary to achieve accurate measurements.

F. Benefits

Subjects participating in the study will receive information regarding their: 1.) lipid and lipoprotein-cholesterol profile, and current recommendations from the National Cholesterol Education Program and the Lipid Clinics' Follow-up Study to help them interpret and understand their test results; 2.) dietary intake of total fat, saturated fat, cholesterol, sodium, fiber, and antioxidants, and current recommendations from the American Dietetics Association to help them understand their dietary assessment; 3.) total and abdominal fat measurements, and comparisons to national normative values and to values associated with increased health risks for women; and 4.) total accumulated time spent in physically active behaviors during a typical week, and recommendations from the United States Surgeon General regarding how much physical activity may be necessary to achieve health-related benefits.

G. Confidentiality

Subject information will only be available to the researcher and research staff of the proposed study. Subjects identity will remain anonymous in the study results by the use of identification numbers instead of names in the data entry and analysis. Confidentiality will be respected regarding the data received in the proposed study.

H. Voluntary Participation

Your participation in the study is completely voluntary and you may withdraw from the study at any time without prejudice.

I. Questions regarding the study

Questions regarding your participation in the study, testing procedures, or any other concerns will be answered by Anthony Wilcox, Ph.D. (principal investigator) (541-737-2463), Jeffrey McCubbin, Ph.D. (principal investigator) (541-737-5921), or Jennifer Slawta, M.S. (investigator) (541-535-8315). Questions regarding your rights as a research subject will be answered by Mary Nunn, Director of Sponsored Programs, OSU Research Office: 541-737-0670.

J. Understanding and Consent

Your signature below indicates that you have read and understand the foregoing and agree to participate in this study. You will receive a copy of this consent form.

_____

Signature of Subject Date Signed

_____

Signature of Investigator Date Signed

APPENDIX C

MODIFIED YALE PHYSICAL ACTIVITY SURVEY

VIGOROUS ACTIVITY

Any activity similar to walking faster than 4.5 mph (fast walking, jogging, swimming laps or exercycling somewhat strenuously)

1. Do you do any vigorous physical activity? _____
2. If yes, what is this vigorous activity?_____

3. How many minutes/hours do you spend doing this activity in a week?_____

<10 minutes = 0
10-30 minutes = 1
31-60 minutes = 2
61-90 minutes = 3
91-120 minutes = 4
121-150 minutes = 5
151-180 minutes = 6
>180 minutes = 7

4. How frequently is this activity performed?_____

None = 0
1-2 days/week = 1
3-4 days/week = 2
5-6 days/week = 3

MODERATE ACTIVITY

Any activity similar to walking briskly (3-4 mph): brisk walking, water aerobics, easy to moderate exercycle or swimming.

1. Do you do any moderate physical activity? _____
2. If yes, what is this moderate activity?_____

3. How many minutes/hours do you spend doing this moderate activity in a week?_____

4. How frequently is this activity performed?_____

LEISURE WALKING/LIGHT ACTIVITY

Any activity similar to walking leisurely (2 mph): leisurely walking, yoga, stretching.

1. Do you do any light activity or leisurely walking?_____
2. If yes, what is this light activity?_____

3. How many minutes/hours do you spend doing this light activity in a week?

4. How frequently is this activity performed?_____

APPENDIX D

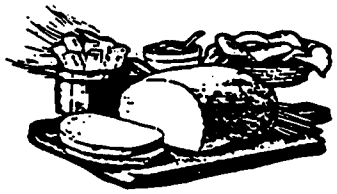
BLOCK FOOD FREQUENCY QUESTIONNAIRE

RESPONDENT ID NUMBER

TODAY'S DATE

	DAY	YEAR
Jan		
Feb		
Mar		1998
Apr		1999
May		2000
Jun		2001
Jul		2002
Aug		2003
Sep		2004
Oct		2005
Nov		2006
Dec		2007

FOOD QUESTIONNAIRE



This form is about the foods you usually eat.
It will take about 30 - 40 minutes to complete.

- Please answer each question as best you can. Estimate if you aren't sure.
- Use only a No. 2 pencil.
- Fill in the circles completely, and erase completely if you make any changes.

Please print your name in this box.

SEX
- Male
- Female

If female, are you pregnant or breast feeding?
- No
- Yes
- Not female

AGE

WEIGHT pounds

HEIGHT ft. in.

First, a few general questions about what you eat.	AVERAGE USE IN THE PAST YEAR								
	LESS THAN ONCE per WEEK	1-2 per WEEK	3-4 per WEEK	5-6 per WEEK	1 per DAY	1 1/2 per DAY	2 per DAY	3 per DAY	4+ per DAY
About how many servings of vegetables do you eat, per day or per week, not counting salad or potatoes?	○	○	○	○	○	○	○	○	○
About how many servings of fruit do you eat, not counting juices?	○	○	○	○	○	○	○	○	○
How often do you eat cold cereal?	○	○	○	○	○	○	○	○	○
How often do you use fat or oil in cooking?	○	○	○	○	○	○	○	○	○

What kinds of fat or oil do you usually use in cooking? MARK ONLY ONE OR TWO

- ○ Don't know, or Pam
- ○ Stick margarine
- ○ Soft tub margarine
- ○ Butter
- ○ Butter/margarine blend
- ○ Low-fat margarine
- ○ Corn oil, vegetable oil
- ○ Olive oil or canola oil
- ○ Lard, fatback, bacon fat
- ○ Crisco

PLEASE DO NOT WRITE IN THIS AREA

18494

During the past year, have you taken any vitamins or minerals regularly, at least once a month?

○ No, not regularly ○ Yes, fairly regularly →

(IF YES) WHAT DID YOU TAKE FAIRLY REGULARLY?

VITAMIN TYPE	HOW OFTEN					FOR HOW MANY YEARS?					
	DIDN'T TAKE	A FEW DAYS per MONTH	1-3 DAYS per WEEK	4-6 DAYS per WEEK	EVERY DAY	LESS THAN 1 YR.	1 YEAR	2 YEARS	3-4 YEARS	5-9 YEARS	10+ YEARS
Multiple Vitamins. Did you take...											
Regular Once-A-Day, Centrum, or Thera type	○	○	○	○	○	○	○	○	○	○	○
Stress-tabs or B-Complex type	○	○	○	○	○	○	○	○	○	○	○
Antioxidant combination type	○	○	○	○	○	○	○	○	○	○	○
Single Vitamins (not part of multiple vitamins)											
Vitamin A (not beta-carotene)	○	○	○	○	○	○	○	○	○	○	○
Beta-carotene	○	○	○	○	○	○	○	○	○	○	○
Vitamin C	○	○	○	○	○	○	○	○	○	○	○
Vitamin E	○	○	○	○	○	○	○	○	○	○	○
Folic acid, folate	○	○	○	○	○	○	○	○	○	○	○
Calcium, alone or combined with something else	○	○	○	○	○	○	○	○	○	○	○
Zinc, alone or combined with something else	○	○	○	○	○	○	○	○	○	○	○
Iron	○	○	○	○	○	○	○	○	○	○	○
Selenium	○	○	○	○	○	○	○	○	○	○	○

If you took Once-a-day, Centrum or Thera-type multiple vitamins, did you usually take types that ○ contain minerals, iron, zinc, etc. ○ do not contain minerals ○ don't know

If you took vitamin C or vitamin E:

How many milligrams of **vitamin C** did you usually take, on the days you took it?
○ 100 ○ 250 ○ 500 ○ 750 ○ 1000 ○ 1500 ○ 2000 ○ 3000+ ○ Don't know

How many IUs of **vitamin E** did you usually take, on the days you took it?
○ 100 ○ 200 ○ 300 ○ 400 ○ 600 ○ 800 ○ 1000 ○ 2000+ ○ Don't know

Did you take any of these supplements at least once a month?

○ Ginkgo ○ Ginseng ○ St. John's Wort ○ Kava Kava ○ Echinacea ○ Melatonin ○ DHEA
○ Glucosamine/Chondroitin ○ Something else ○ Didn't take these

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The next section is about your <u>usual</u> eating habits in the past year or so. This includes all meals or snacks, at home or in a restaurant or carry-out. There are two kinds of questions to answer for each food:

HOW OFTEN, on average, did you eat the food during the past year?
*Please DO NOT SKIP any foods. Mark "Never" if you didn't eat it.

HOW MUCH did you usually eat of the food?

*Sometimes we ask how <u>many</u> you eat, such as 1 egg, 2 eggs, etc., ON THE DAYS YOU EAT IT.
*Sometimes we ask "how much" as A, B, C or D. LOOK AT THE ENCLOSED PICTURES. For each food, pick the picture (bowls or plates) that looks the most like the serving size you usually eat.
(If you don't have pictures: A=1/4 cup, B=1/2 cup, C=1 cup, D=2 cups.)
*Sometimes we made the "D" column a darker color. This is just to remind you to make sure you really eat that large a serving.

EXAMPLE: This person drank apple juice twice a week, and had one glass each time. Once a week he ate a "C" sized serving of rice (about 1 cup).

HOW OFTEN	NEVER	A FEW TIMES per YEAR	ONCE per MON.	2-3 TIMES per MON.	ONCE per WEEK	TWICE per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	HOW MUCH <u>EACH TIME</u> SEE PORTION SIZE PICTURES FOR A-B-C-D				
Apple juice	○	○	○	○	○	●	○	○	○	How many glasses each time	● 1	○ 2	○ 3	○ 4
Rice	○	○	○	○	●	○	○	○	○	How much each time	○ A	○ B	● C	○ D

HOW OFTEN	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	2 TIMES per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	HOW MUCH EACH TIME How many glasses on the days you drink it?
How often do you drink the following beverages?										
Tomato juice or V-8 juice	○	○	○	○	○	○	○	○	○	How many glasses each time ○1 ○2 ○3 ○4
Real 100% orange juice or grapefruit juice, including fresh, frozen or bottled	○	○	○	○	○	○	○	○	○	How many glasses each time ○1 ○2 ○3 ○4
When you drink orange juice, how often do you drink a calcium-fortified brand?	○ Usually calcium-fortified ○ Sometimes calcium-fortified ○ Hardly ever calcium-fortified ○ I don't know ○ I don't drink orange juice									
Other real fruit juices like apple juice, prune juice, lemonade	○	○	○	○	○	○	○	○	○	How many glasses ○1 ○2 ○3 ○4
Kool-Aid, Hi-C, or other drinks with added vitamin C	○	○	○	○	○	○	○	○	○	How many glasses ○1 ○2 ○3 ○4
Drinks with some juice in them, like Sunny Delight, Juice Squeeze	○	○	○	○	○	○	○	○	○	How many bottles ○1 ○2 ○3 ○4
Instant breakfast milkshakes like Carnation, diet shakes like SlimFast, or liquid supplements like Ensure	○	○	○	○	○	○	○	○	○	How many glasses or cans ○1 ○2 ○3 ○4
Glasses of milk (any kind)	○	○	○	○	○	○	○	○	○	How many glasses ○1 ○2 ○3 ○4

When you drink glasses of milk, what kind do you usually drink? **MARK ONLY ONE:**

○ Whole milk ○ Reduced-fat 2% milk ○ Low-fat 1% milk ○ Non-fat milk
○ Rice milk ○ Soy milk ○ I don't drink milk or soy milk

HOW OFTEN	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	2 TIMES per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	HOW MUCH EACH TIME
Regular soft drinks, or bottled drinks like Snapple (not diet drinks)	○	○	○	○	○	○	○	○	○	How many bottles or cans ○1 ○2 ○3 ○4
Beer or non-alcoholic beer	○	○	○	○	○	○	○	○	○	How many bottles or cans ○1 ○2 ○3 ○4
What kind? **MARK ONLY ONE:** ○ Regular beer ○ Light beer ○ Non-alcoholic beer ○ I don't drink beer										
Wine or wine coolers	○	○	○	○	○	○	○	○	○	How many glasses ○1 ○2 ○3 ○4
Liquor or mixed drinks	○	○	○	○	○	○	○	○	○	How many drinks ○1 ○2 ○3 ○4
Glasses of water, tap or bottled	○	○	○	○	○	○	○	○	○	How many glasses ○1 ○2 ○3 ○4
Coffee, regular or decaf	○	○	○	○	○	○	○	○	○	How many cups ○1 ○2 ○3 ○4
Tea or iced tea (not herb teas)	○	○	○	○	○	○	○	○	○	How many cups ○1 ○2 ○3 ○4

What do you usually add to coffee? **MARK ONLY ONE:** ○ Cream or half & half ○ Nondairy creamer ○ Milk ○ None of these

What do you usually add to tea? **MARK ONLY ONE:** ○ Cream or half & half ○ Nondairy creamer ○ Milk ○ None of these

Do you usually add sugar (or honey) to coffee? ○ No ○ Yes IF YES, how many teaspoons each cup? ①②③④

Do you usually add sugar (or honey) to tea? ○ No ○ Yes IF YES, how many teaspoons each cup? ①②③④

18494

PLEASE DO NOT WRITE IN THIS AREA

HOW OFTEN	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	2 TIMES per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	HOW MUCH EACH TIME — SEE PORTION SIZE PICTURES FOR A-B-C-D
How often do you eat each of the following fruits, just during the 2-3 months when they are in season?										
Raw peaches, apricots, nectarines, while they are in season	○	○	○	○	○	○	○	○	○	How many each time: ○ 1/2 ○ 1 ○ 2 ○ 3
Cantaloupe, in season	○	○	○	○	○	○	○	○	○	How much: ○ 1/8 ○ 1/4 ○ 1/2 ○ 1
Strawberries, in season	○	○	○	○	○	○	○	○	○	How much: ○ A ○ B ○ C ○ D
Watermelon, in season	○	○	○	○	○	○	○	○	○	How much: ○ A ○ B ○ C ○ D
Any other fruit in season, like grapes, honeydew, pineapple, kiwi	○	○	○	○	○	○	○	○	○	How much: ○ A ○ B ○ C ○ D
How often do you eat the following foods all year round? Estimate your average for the whole year.										
Bananas	○	○	○	○	○	○	○	○	○	How many each time: ○ 1/2 ○ 1 ○ 2 ○ 3
Apples or pears	○	○	○	○	○	○	○	○	○	How many each time: ○ 1/2 ○ 1 ○ 2 ○ 3
Oranges or tangerines	○	○	○	○	○	○	○	○	○	How many each time: ○ 1/2 ○ 1 ○ 2 ○ 3
Grapefruit	○	○	○	○	○	○	○	○	○	How much: ○ 1/2 ○ 1 ○ 2 ○ 3
Canned fruit like applesauce, fruit cocktail, or dried fruit like raisins	○	○	○	○	○	○	○	○	○	How much: ○ A ○ B ○ C ○ D

HOW OFTEN	NEVER	FEW/ YEAR	ONCE/ MONTH	2-3 TIMES/ MONTH	ONCE/ WEEK	TWICE/ WEEK	3-4 TIMES/ WEEK	5-6 TIMES/ WEEK	EVERY DAY	HOW MUCH EACH TIME
Eggs, including egg biscuits or Egg McMuffins (Not egg substitutes)	○	○	○	○	○	○	○	○	○	How many eggs each time: ○ 1 ○ 2 ○ 3 ○ 4
Bacon	○	○	○	○	○	○	○	○	○	How many pieces: ○ 1 ○ 2 ○ 3 ○ 4
Breakfast sausage, including sausage biscuits	○	○	○	○	○	○	○	○	○	How many pieces: ○ 1 ○ 2 ○ 3 ○ 4
Pancakes, waffles, French toast, Pop Tarts	○	○	○	○	○	○	○	○	○	How many pieces: ○ 1 ○ 2 ○ 3 ○ 4
Breakfast bars, granola bars, Power bars	○	○	○	○	○	○	○	○	○	How many: ○ 1 ○ 2 ○ 3 ○ 4
Cooked cereals like oatmeal, cream of wheat or grits	○	○	○	○	○	○	○	○	○	Which bowl: ○ B ○ C ○ D
High-fiber cereals like All Bran, Raisin Bran, Fruit-n-Fiber	○	○	○	○	○	○	○	○	○	Which bowl: ○ B ○ C ○ D

Which high-fiber cereal do you eat most often? **MARK ONLY ONE:** ○ All Bran or Bran Buds ○ Raisin Bran ○ Fiber One, Fruit-n-Fiber, etc. ○ Something else ○ I don't know ○ I don't eat it

Product 19, Just Right or Total cereal	○	○	○	○	○	○	○	○	○	Which bowl: ○ B ○ C ○ D
Any other cold cereal, like Corn Flakes, Cheerios, Special K	○	○	○	○	○	○	○	○	○	Which bowl: ○ B ○ C ○ D
Milk or milk substitutes on cereal	○	○	○	○	○	○	○	○	○	How many oz. on cereal: ○ 3 oz. ○ 4-5 oz. ○ 6-7 oz. ○ 8+ oz.
Yogurt or frozen yogurt	○	○	○	○	○	○	○	○	○	How much: ○ A ○ B ○ C ○ D
Cheese, sliced cheese or cheese spread, including on sandwiches	○	○	○	○	○	○	○	○	○	How many slices: ○ 1 ○ 2 ○ 3 ○ 4

When you eat cheese, is it ○ Usually low-fat ○ Sometimes low-fat ○ Hardly ever low-fat ○ Don't know/don't eat

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HOW OFTEN	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	2 TIMES per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	HOW MUCH EACH TIME SEE PORTION SIZE PICTURES FOR A-B-C-D
How often do you eat the following vegetables, including fresh, frozen, canned or in stir-fry, at home or in a restaurant?										
Broccoli	○	○	○	○	○	○	○	○	○	How much A B C D
Carrots, or mixed vegetables or stews containing carrots	○	○	○	○	○	○	○	○	○	How much A B C D
Corn	○	○	○	○	○	○	○	○	○	How much A B C D
Green beans or green peas	○	○	○	○	○	○	○	○	○	How much A B C D
Spinach	○	○	○	○	○	○	○	○	○	How much A B C D
Mustard greens, turnip greens, collards	○	○	○	○	○	○	○	○	○	How much A B C D
French fries, fried potatoes or hash browns	○	○	○	○	○	○	○	○	○	How much A B C D
White potatoes not fried, incl. boiled, baked, mashed & potato salad	○	○	○	○	○	○	○	○	○	How much A B C D
Sweet potatoes, yams (Not in pie)	○	○	○	○	○	○	○	○	○	How much A B C D
Cole slaw, cabbage	○	○	○	○	○	○	○	○	○	How much A B C D
Green salad	○	○	○	○	○	○	○	○	○	How much A B C D
Raw tomatoes, including in salad	○	○	○	○	○	○	○	○	○	How much 1/4 1/2 1 2
Salad dressing	○	○	○	○	○	○	○	○	○	How many Tbsp. 1 2 3 4

Is your salad dressing ○ Usually low-fat ○ Sometimes low-fat ○ Hardly ever low-fat ○ Don't know/don't use

HOW OFTEN	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	2 TIMES per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	HOW MUCH EACH TIME
Any other vegetable, like okra, squash, cooked green peppers	○	○	○	○	○	○	○	○	○	How much A B C D
Refried beans or bean burritos	○	○	○	○	○	○	○	○	○	How much A B C D
Chili with beans (with or without meat)	○	○	○	○	○	○	○	○	○	How much A B C D
Baked beans, black-eye peas, pintos, any other dried beans	○	○	○	○	○	○	○	○	○	How much A B C D
Vegetable stew	○	○	○	○	○	○	○	○	○	Which Bowl B C D
Vegetable soup, vegetable beef, chicken vegetable, or tomato soup	○	○	○	○	○	○	○	○	○	Which Bowl B C D
Split pea, bean or lentil soup	○	○	○	○	○	○	○	○	○	Which Bowl B C D
Any other soup, like chicken noodle, chowder, mushroom, instant soups	○	○	○	○	○	○	○	○	○	Which Bowl B C D
Spaghetti, lasagna or other pasta with tomato sauce	○	○	○	○	○	○	○	○	○	How much A B C D
Cheese dishes without tomato sauce, like macaroni and cheese	○	○	○	○	○	○	○	○	○	How much A B C D
Pizza, including carry-out	○	○	○	○	○	○	○	○	○	How many slices 1 2 3 4

HOW OFTEN	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	2 TIMES per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	HOW MUCH EACH TIME SEE PORTION SIZE PICTURES FOR A-B-C-D
Do you ever eat chicken, meat or fish? ⊃ Yes ⊃ No **IF NO, SKIP TO NEXT PAGE**										
Hamburgers, cheeseburgers, meat loaf, at home or in a restaurant	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	How much meat ⊃ 1/8 lb. ⊃ 1/4 lb ⊃ 1/2 lb. ⊃ 3/4 lb
Tacos, burritos, enchiladas, tamales, etc. with meat or chicken	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	How much ⊃ A ⊃ B ⊃ C ⊃ D
Beef steaks, roasts, pot roast, or in frozen dinners or sandwiches	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	How much ⊃ A ⊃ B ⊃ C ⊃ D
How do you like beef cooked? ⊃ Rare ⊃ Medium ⊃ Well done ⊃ I don't eat beef										
Pork chops, pork roasts, or dinner ham	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	How much ⊃ A ⊃ B ⊃ C ⊃ D
When you eat meat, do you ⊃ Avoid eating the fat ⊃ Sometimes eat the fat ⊃ Often eat the fat ⊃ I don't eat meat										
Veal, lamb or deer meat	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	How much ⊃ A ⊃ B ⊃ C ⊃ D
Ribs, spareribs	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	How many ribs ⊃ 3-4 ⊃ 5-6 ⊃ 7-8 ⊃ 9+
Liver, including chicken livers or liverwurst	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	How much ⊃ A ⊃ B ⊃ C ⊃ D
Gizzard, pork neckbones, chitlins, pigs feet, etc.	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	How much ⊃ A ⊃ B ⊃ C ⊃ D
Mixed dishes with beef or pork, like stew, corned beef hash, stuffed cabbage, meat dish with noodles	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	⊃	How much ⊃ A ⊃ B ⊃ C ⊃ D
Mixed dishes with chicken, like chicken casserole, chicken & noodles, pot pie or in stir-fry	○	○	○	○	○	○	○	○	○	How much ○ A ○ B ○ C ○ D
Fried chicken, at home or in a restaurant	○	○	○	○	○	○	○	○	○	# medium pieces ○ 1 ○ 2 ○ 3 ○ 4
Chicken or turkey not fried, such as baked, grilled, or on sandwiches	○	○	○	○	○	○	○	○	○	How much ○ A ○ B ○ C ○ D
When you eat chicken, do you ○ Avoid eating the skin ○ Sometimes eat the skin ○ Often eat the skin										

HOW OFTEN	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	2 TIMES per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	HOW MUCH EACH TIME
Oysters	○	○	○	○	○	○	○	○	○	How much ○ A ○ B ○ C ○ D
Other shellfish like shrimp, scallops, crabs	○	○	○	○	○	○	○	○	○	How much ○ A ○ B ○ C ○ D
Tuna, tuna salad, tuna casserole	○	○	○	○	○	○	○	○	○	How much of the tuna ○ A ○ B ○ C ○ D
Fried fish or fish sandwich, at home or in a restaurant	○	○	○	○	○	○	○	○	○	How much ○ A ○ B ○ C ○ D
Other fish, not fried	○	○	○	○	○	○	○	○	○	How much ○ A ○ B ○ C ○ D
Hot dogs, or sausage like Polish, Italian or chorizos	○	○	○	○	○	○	○	○	○	How many ○ 1 ○ 2 ○ 3 ○ 4
Are your hot dogs ○ Usually low-fat ○ Sometimes low-fat ○ Hardly ever low-fat ○ Don't know/don't eat them										
Boloney, sliced ham, turkey lunch meat, other lunch meat	○	○	○	○	○	○	○	○	○	How many slices ○ 1 ○ 2 ○ 3 ○ 4
Are your lunch meats ○ Usually low-fat or turkey ○ Sometimes low-fat ○ Hardly ever low-fat										

HOW OFTEN	NEVER	A FEW TIMES per YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	2 TIMES per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	HOW MUCH EACH TIME — SEE PORTION SIZE PICTURES FOR A-B-C-D
Noodles, macaroni, pasta salad	○	○	○	○	○	○	○	○	○	How much A B C D
Tofu, bean curd	○	○	○	○	○	○	○	○	○	How much A B C D
Meat substitutes, such as veggie burgers, Gardenburgers	○	○	○	○	○	○	○	○	○	How many patties 1 2 3 4
Chinese food, Thai or other Asian food, not counted above	○	○	○	○	○	○	○	○	○	How much A B C D
Snacks like potato chips, corn chips, popcorn (not pretzels)	○	○	○	○	○	○	○	○	○	How much A B C D

Are these snacks ○ Usually low-fat ○ Sometimes low-fat ○ Hardly ever low-fat ○ Don't know/don't eat

HOW OFTEN	NEVER	FEW/ YEAR	ONCE/ MONTH	2-3 TIMES/ MONTH	ONCE/ WEEK	2 TIMES/ WEEK	3-4 TIMES/ WEEK	5-6 TIMES/ WEEK	EVERY DAY	HOW MUCH EACH TIME
Peanuts, other nuts or seeds	○	○	○	○	○	○	○	○	○	How much A B C D
Crackers	○	○	○	○	○	○	○	○	○	How much A B C D
Doughnuts, Danish pastry	○	○	○	○	○	○	○	○	○	How many 1 2 3 4
Cake, sweet rolls, coffee cake	○	○	○	○	○	○	○	○	○	How much A B C D

Are they ○ Usually low-fat ○ Sometimes low-fat ○ Hardly ever low-fat ○ Don't know/don't eat

Cookies	○	○	○	○	○	○	○	○	○	How many 1-2 3-5 6-7 8+

Are your cookies ○ Usually low-fat ○ Sometimes low-fat ○ Hardly ever low-fat ○ I don't know/don't eat

Ice cream, ice milk, ice cream bars	○	○	○	○	○	○	○	○	○	How much A B C D

Is your ice cream ○ Usually low-fat ○ Sometimes low-fat ○ Hardly ever low-fat ○ I don't know/don't eat

Pumpkin pie, sweet potato pie	○	○	○	○	○	○	○	○	○	How many slices 1/2 1 2 3
Any other pie or cobbler	○	○	○	○	○	○	○	○	○	How many slices 1/2 1 2 3
Chocolate candy, candy bars	○	○	○	○	○	○	○	○	○	How many bars small medium large large
Other candy, not chocolate, like hard candy, caramel, jelly beans	○	○	○	○	○	○	○	○	○	How many pieces 1-2 3-5 6-7 8+

[illegible]

HOW OFTEN	NEVER OR A FEW TIMES PER YEAR	ONCE per MONTH	2-3 TIMES per MONTH	ONCE per WEEK	2 TIMES per WEEK	3-4 TIMES per WEEK	5-6 TIMES per WEEK	EVERY DAY	2+ TIMES per DAY	HOW MUCH EACH TIME — SEE PORTION SIZE PICTURES FOR A-B-C-D				
Biscuits or muffins	○	○	○	○	○	○	○	○	○	How many each time	1	2	3	4
Rolls, hamburger buns, English muffins, bagels	○	○	○	○	○	○	○	○	○	How many each time	1/2	1	2	3
Dark bread like rye or whole wheat, including in sandwiches	○	○	○	○	○	○	○	○	○	How many slices each time	1	2	3	4
White bread or toast, including French, Italian, or in sandwiches	○	○	○	○	○	○	○	○	○	How many slices each time	1	2	3	4
Corn bread, corn muffins	○	○	○	○	○	○	○	○	○	How many pieces	1	2	3	4
Tortillas	○	○	○	○	○	○	○	○	○	How many each time	1	2	3	4
Rice, or dishes made with rice	○	○	○	○	○	○	○	○	○	How much	A	B	C	D
Margarine (not butter) on bread or on potatoes or vegetables, etc.	○	○	○	○	○	○	○	○	○	How many pats (tsp.)	1	2	3	4
Butter (not margarine) on bread or on potatoes or vegetables, etc.	○	○	○	○	○	○	○	○	○	How many pats (tsp.)	1	2	3	4
Gravy	○	○	○	○	○	○	○	○	○	How many Tbsp.	1	2	3	4
Peanut butter	○	○	○	○	○	○	○	○	○	How many Tbsp.	1	2	3	4
Jelly, jam, or syrup	○	○	○	○	○	○	○	○	○	How many Tbsp.	1	2	3	4
Mayonnaise, sandwich spreads	○	○	○	○	○	○	○	○	○	How many Tbsp.	1	2	3	4
Catsup, salsa or chile peppers	○	○	○	○	○	○	○	○	○	How many Tbsp.	1	2	3	4
Mustard, soy sauce, steak sauce, barbecue sauce, other sauces	○	○	○	○	○	○	○	○	○	How many Tbsp.	1	2	3	4

Did you use the pictures to choose your serving size on this form? ○ Yes ○ No ○ I didn't have any pictures.

Would you say your health is ○ Excellent ○ Very good ○ Good ○ Fair ○ Poor

How many times have you gone on a diet? ○ Never ○ 1-2 ○ 3-5 ○ 6-8 ○ 9 or more

Did you ever drink more beer, wine or liquor than you do now? ○ Yes ○ No

How many hours do you watch television or video, per day or per week on average?
○ None ○ 1-6 hours/week ○ 1 hour/day ○ 2 hours/day ○ 3 hours/day ○ 4+ hours/day

Do you smoke cigarettes now? ○ No ○ Yes
IF YES, On the average about how many cigarettes a day do you smoke now?
○ 1-5 ○ 6-14 ○ 15-24 ○ 25-34 ○ 35 or more

What language do you usually speak at home or with friends?
○ English ○ Spanish ○ Something else ○ English & something else equally

What is your ethnic group? (MARK ONE OR MORE)
○ Hispanic or Latino ○ Black or African American ○ American Indian or Alaska Native
○ White, not Hispanic ○ Asian ○ Native Hawaiian or Other Pacific Islander

[redacted] for filling out this questionnaire. Please take a minute to go back and fill in anything you may have skipped.

PLEASE DO NOT WRITE IN THIS AREA

18494

APPENDIX E

MEDICAL HISTORY QUESTIONNAIRE

Medical History Questionnaire

Personal History

Are you currently employed? _____(no) _____(yes)

How many years since your diagnosis with MS?_____

Personal Habits

Do you currently smoke? _____(no)_____(yes)
If yes, how many cigarettes do you smoke each day? _____
If no, have you ever smoked cigarettes in the past? _____(no)_____(yes)
If yes, indicate when did you quit smoking_____
Do you currently drink alcohol?_____(no)_____(yes)
If yes, how many alcoholic drinks do you drink per day?_____week?_____month?_____

Personal Medical History

Have you gone through menopause_____(no)_____(yes)
If yes, at what age?_____

Medications

Current medication use	No	Yes (name/dose)
Insulin or other diabetic medications		
Thyroid medications		
Gout or uric acid-lowering medications		
Corticosteroids		
Blood pressure medications		
Cholesterol-lowering medications		
Hormone replacement therapy		

Mobility

Check one of the following boxes which best describes your level of mobility	X
I have no restriction on activities of normal employment or domestic life, but I am not necessarily symptom-free.	
I am able to walk on level surfaces using no aids for short distances only (for about 15 minutes) before I must stop and rest.	
I am able to walk alone but must use aids (walls, furniture, cane crutches, walker, or braces).	
I can walk a few steps but usually use a wheelchair.	
I use a wheelchair and cannot walk, but I have the ability to transfer.	
I use a wheelchair exclusively, and I cannot transfer.	
I must be in bed all or most of the time.	

APPENDIX F

POSTMENOPAUSAL ESTROGENS/PROGESTINS INTERVENTION PHYSICAL ACTIVITY QUESTIONNAIRE

The Postmenopausal Estrogens/Progestins Intervention Physical Activity Questionnaire

For *a* through *c* below, use the following as a guide to describe your activity level:

1. **Physical Inactivity:** The inactive person spends most waking hours sitting or standing quietly. Activities include working at a desk, reading, watching television, or other quiet pursuits. Usually does not walk more than a few minutes.

2. **Light Physical Activity:** This person usually walks more than 10 minutes at a time each day, leisurely rides a bicycle, fishes, bowls, golfs, or engages in light carpentry, light gardening, light industrial work, teaching, or light house work on a regular basis.

3. **Moderate Physical Activity:** This person participates in such activities as brisk walking, recreational or doubles tennis, or swimming; or works in such occupations as mail carrier, telephone repair, light building, and construction; or engages in housework and home repairs or moderate gardening.

4. **Heavy Physical Activity:** This person performs vigorous activity on a regular basis, including jogging, singles tennis, paddleball, or high-intensity aerobics; or engages in heavy activities, such as carrying heavy weights (20 lb. or more), strenuous farm work, or strenuous gardening.

ID#: _____

a. Thinking about the things you usually did *at work* during the last 12 months, how would you describe the kind of physical activity you performed?

_____Inactive _____Light ____Moderate ____Heavy ____Not applicable

b. Thinking about the things you usually did *in your home* during the last 12 months, how would you describe the kind of physical activity you performed?

_____Inactive _____Light _____Moderate _____Heavy

c. Thinking about the things you usually did *in your leisure time* during the last 12 months, how would you describe the kind of physical activity you performed?

_____Inactive _____Light _____Moderate _____Heavy

APPENDIX G

LITERATURE REVIEW

Introduction

CHD contributes to the majority of deaths among men and women in the United States (36). Physical inactivity is designated as a major risk factor for CHD (36,82,109,123). Physically inactive individuals are 1.5 to 2.4 times more likely to develop CHD relative to physically active individuals (82). Women with MS are frequently less active than sedentary women without MS (76,87), yet some women with MS remain physically active despite their disability. However, it is unknown whether women with MS are able to participate in enough activity to achieve health-related benefits and to reduce their CHD risk.

Although CHD is equally prevalent in men and women, the relative contribution of risk factors for CHD differ between men and women. For instance, high circulating levels of TG and low circulating levels of HDL-C are more important predictors of CHD risk in women when compared with men (72). Furthermore, among women, high TG levels and low HDL-C levels are stronger predictors for CHD than high levels of total cholesterol LDL-C (72).

Abdominal fat gain and insulin resistance are believed to precede and be largely responsible for CHD risk-related increases in circulating levels of TG and CHD risk-related reductions in HDL-C (21,24,57). In this regard, high lipolytic activity of abdominal fat cells increases free fatty acid (FFA) flux to the liver, which in turn, impairs hepatic insulin extraction, thus contributing to hyperinsulinemia and insulin resistance (41,96,98). Insulin resistant-related alterations in the activities of the lipoprotein enzymes are ultimately responsible for higher circulating levels of TG and lower circulating levels of HDL-C (7,24,41,98). Therefore, obesity, in particular, abdominal obesity is a major risk factor for insulin resistance and CHD.

The first section of the literature review will introduce MS and address the etiology, epidemiology, and medical treatments associated with MS. Because insulin resistance is believed to precede and be largely responsible for CHD-related metabolic disorders including high circulating levels of TG and low circulating levels of HDL-C (21,24,53), *the second section of the literature review will address insulin resistance and its biological association with high TG levels and low HDL-C levels.*

Physical activity reduces the risk for CHD, in part, by lowering total and abdominal fat, improving insulin resistance, lowering plasma TG levels, and raising plasma HDL-C levels (21,82,100,123,124). Thus, *the third section of the literature review will address the influence of physical activity on the insulin-resistant CHD metabolic profile.* Because reductions in physical activity frequently accompany aging, consistent participation in physical activity may, perhaps, prevent some of the age-related increases in obesity and its associated metabolic and hormonal disorders.

The symptoms of MS can interfere with and limit life activities in persons with MS. Furthermore, several perceived barriers prohibit participation in physical activity by persons with MS including fatigue, mobility transportation, fear, and overheating (113,114,115). However, current physical activity guidelines endorsed by the United States Surgeon General (123) and the American Heart Association (109), which recommend a broad range of frequent bouts of moderate-intensity physical activity accumulating 30 minutes each day may be attainable by persons with MS. Thus, *the fourth section of the literature review will address physical activity in persons with MS, and the role that nonvigorous, moderate-intensity physical activity can have on improving physical functioning and reducing CHD risk in persons with MS.*

The Etiology and Epidemiology of Multiple Sclerosis

There are currently between 250,000 and 400,000 physician-diagnosed cases of MS in the United States (3,103), and 8000 new cases are diagnosed each year (87). Because MS is difficult to diagnose, and because there are no concrete diagnostic tests for MS, the incidence of MS is likely to be greater than 400,000 (87). In fact, autopsy studies suggest the incidence of MS to be two times higher than prevalence estimations of MS based on physician diagnosis (103).

There is a gender, genetic, and geographical predisposition towards MS. In this regard, women are twice as likely to develop MS relative to men (87,89,102,103,114), a child born to a parent with MS is at a slightly greater risk (2-4%) for developing MS during his/her life, and the occurrence of MS is more prevalent in geographical regions located farther away from the equator (87,102,103). Furthermore, 95% of persons with MS are Caucasian (102,103,114) and there is a slightly greater tendency for MS among the higher socioeconomic classes (103).

MS may be diagnosed as exacerbating/remitting, chronic progressive, or a combination of exacerbating/remitting and chronic progressive (87,89). Prevention of MS is unknown and clinical management of MS is difficult (103,114). Early MS frequently begins as exacerbating/remitting and overtime may develop into chronic progressive (87,103). The clinical course of the disease with regard to the severity of symptoms, exacerbations, and progressions is highly variable from patient to patient (87,103,114). Although a small percent of persons with MS may experience a very rapid, progressive deterioration (87,114), the majority of persons with MS will live 90% of a full life span and the majority of these persons will remain ambulatory (87,103,114).

MS is an autoimmune disorder by which the body's immune system mistakenly attacks and destroys the myelin sheaths surrounding and insulating axons of neurons in the CNS (87,102,103). Myelin is primarily composed of lipid and is responsible for promoting smooth muscle conduction of electrical impulses in the CNS (103). The essential fatty acids, linoleic acid and linolenic acid, predominate in the lipid fraction of myelin and are important nutrients necessary for brain growth and maintenance (18,74,121). Communication between neurons in the CNS occurs in the form of action

potentials. Action potentials are generated at the nodes of Ranvier which interrupt the layering of myelin at periodic intervals along the length of the axon (11,70). Because action potentials do not occur in myelinated areas, the nodes of Ranvier permit the action potential to jump from node to node as it propagates along a myelinated fiber (11,70). This type of conduction is termed 'saltatory' conduction, meaning conduction that leaps.

In early MS, the blood brain barrier is damaged by activated T cells which mount a cell-mediated immune attack on myelin and the myelin producing cells, oligodendrocytes (87,103). Plaque replaces myelin and contributes to the symptoms of MS (75). The specific antigen under attack is believed to be immunodominant myelin basic protein and/or target sites on the surface of the oligodendrocytes (87). Because the immune system-mediated demyelination begins at the nodes of Ranvier, the conduction of current is impaired leading to a reduced conduction rate and, in more severe cases, a complete block of conduction (87,103). Areas of demyelination in the CNS are depicted by white spots with magnetic resonance imaging (103). Inflammation results from the immune system's attack on myelin, which in turn, causes edema and interference with nerve conduction in non-demyelinating neurons lying in close proximity to the areas of demyelination (103). Remyelination allows for some replacement of myelin and activation of oligodendrocytes damaged during the demyelination process (87). However, the replaced myelin is thin with more nodes of Ranvier relative to the original myelin (87).

Symptoms associated with MS, including fatigue, ataxia, spasticity, muscle weakness, dizziness, numbness, clumsiness, slurred speech, blurred vision, and lack of bladder control, are most often experienced between the ages of 20 and 40 (87,89,103,114), but are known to occur in children and the elderly (87). Lower extremity movement is more frequently disturbed by MS than upper extremity movement (89). The symptoms of MS profoundly interfere with and limit life activities in persons with MS. In fact, MS restricts life activities to a greater extent than any other chronic disabling condition (89).

Although MS is known to be primarily an autoimmune disorder, viral infections (103) and nutritional factors (18,74,121) are hypothesized to contribute to the development of MS. For instance, viral infections are believed to contribute to the onset

of MS by triggering the immune system's attack against susceptible myelin (103). Furthermore, exacerbations of the disease frequently follow a viral infection (87,103). Because essential fatty acids are critical for brain growth and development, and because essential fatty acids are principle components of myelin (18,74,121), reductions in dietary intake of essential fatty acids or altered essential fatty acid absorption and metabolism during a critical period in early brain development may increase the susceptibility of the CNS to demyelination in later life (18).

The incidence of MS is geographically greater in populations consuming diets high in saturated fat and diets low in essential fats (1,18). In contrast, populations with rich intakes of essential fatty acids have low rates of MS. In fact, MS is nonexistant in Eskimos (103), a population known to consume high dietary amounts of essential fatty acids from the predominance of fish in their diets. Furthermore, reductions in the severity and frequency of exacerbations, and reductions in overall deterioration, are observed when saturated fat is replaced with polyunsaturated fat (117). Levels of essential fatty acids in the blood of persons with MS are frequently low, and reduced levels of unsaturated fatty acids and elevated levels of saturated fatty acids are frequently observed in the white matter of brains dissected from persons with MS (121). Levels of linoleic acid contained in circulating lipoproteins are frequently reduced in persons with MS (74,121) and replaced with saturated fat, primarily palmitic acid (74). Furthermore, levels of linoleic acid in circulating lipoproteins are progressively reduced with deterioration of the disease (74,121). One explanation for the lower levels of circulating essential fatty acids in persons with MS may be that a large proportion of essential fatty acids are used for the synthesis of prostaglandins (74) involved in the inflammatory response associated with MS. Linoleic supplementation may reduce the severity and duration of exacerbations, and the progression of disability in MS patients with mild or no disability (33). The mechanism by which linoleic acid supplements may reduce the progression of MS is not known. However, it is hypothesized that linoleic-derived prostaglandins suppress the immune system's attack on myelin (33).

Several medications are available to ameliorate the symptoms associated with MS and to improve the functioning of persons with MS. Corticosteroids reduce inflammation in the CNS associated with exacerbations (87,103). Evidence suggests that the majority

of women with MS (>60%) have undergone at least two courses of corticosteroid treatment (114). A high dose of corticosteroids for a short period of time is recommended to reduce the duration and severity of exacerbations. However, extended period of corticosteroid use may increase the risk for osteoporosis, diabetes, and CHD (87).

Betaseron (Interferon B), a synthetic protein structurally similar to myelin basic protein, is effective in reducing the severity and duration of exacerbations primarily in persons with exacerbating/remitting MS, but may also be effective in some persons with chronic progressive MS (87,103). A number of medications are currently available to reduce spasticity in persons with MS including baclofen, diazepam (valium), clonazapam (klonopin), dantrolene (dantrium), back spasm medications, and carbamazepine (tegretol) (103). Hytrin and dibenzyline are alpha-blockers that are frequently prescribed for bladder control (103).

Insulin Resistance and its Contribution to High Plasma Levels of TG and Low Plasma Levels of HDL-C

Insulin is an important hormone in the regulation of blood glucose levels. Insulin is secreted from the beta cells in the pancreas in response to high circulating blood glucose concentrations following a meal, and is responsible for mediating glucose disposal into target tissues of the body. Abnormally high blood glucose concentrations are suggestive of a disturbance in insulin sensitivity, characterized by an impairment in glucose disposal into target tissues, and/or a disturbance in insulin response, characterized by an impairment in insulin secretion from the beta cells.

Insulin-dependent diabetes mellitus (IDDM), or type 1 diabetes is manifested by an impairment in beta cell secretion of insulin and accounts for 10% of the American population diagnosed with diabetes (100). By contrast, insulin resistance is characterized by a deterioration in insulin sensitivity in peripheral tissues and an increase in hepatic glucose output, which in turn, leads to higher plasma glucose levels (hyperglycemia), an increase in insulin secretion from the pancreas to compensate for the hyperglycemia , and ultimately the development of noninsulin-dependent diabetes mellitus (NIDDM), or type 2 diabetes (96,98). NIDDM accounts for 90% of the American population diagnosed with diabetes (100). Furthermore, insulin resistance is believed to precede and be largely responsible for CHD-related metabolic disorders including high plasma TG levels and low HDL-C levels (21,24,57). Thus, insulin resistance is believed to be the initial metabolic disorder in the development of NIDDM and CHD (21,24,26).

Evidence from the Framingham study suggest that the risk for cardiovascular disease is three times higher in diabetic women and two times higher in diabetic men relative to their nondiabetic counterparts (55). Although a large portion of the increased CHD risk among diabetics may be attributed to the presence of established CHD risk factors, including high TG levels and low HDL-C levels, a significant portion of the increased CHD risk among diabetic patients is not entirely explained by increases in CHD risk factors (41). In fact, insulin resistance and compensatory hyperinsulinemia increase the risk for ischemic heart disease (23) and CHD-related events (i.e., non-fatal

myocardial infarction or CHD death) (94) independently from their relationship with other known biological CHD risk factors.

High blood glucose levels, representative of 'full-blown' NIDDM, ultimately result from the combination of a deterioration in insulin sensitivity and a reduction in glucose-mediated insulin secretion from the pancreatic beta cell (9,96,98). In the early stages of insulin resistance, the beta cell may secrete large amounts of insulin to compensate for a deterioration in insulin sensitivity in an attempt to maintain normal blood glucose levels (9,96,98,124). Thus, the onset of insulin resistance may initially be characterized by elevated circulating insulin levels (compensatory hyperinsulinemia). In fact, insulin resistant individuals frequently have normal levels of fasting glucose due to the ability of the pancreas to secrete large amounts of insulin necessary to overcome the resistance of the body's tissues to insulin (96,98). The pancreas will continue to secrete more and more insulin in response to a progressive deterioration in insulin sensitivity and greater blood glucose levels. Therefore, the degree of insulin resistance may be best determined by measuring circulating concentrations of insulin. In the latter stages of insulin resistance, however, insulin stores may become depleted, such that the pancreas may cease to secrete enough insulin to maintain normal blood glucose levels (9,96,124), which in turn, leads to high circulating blood glucose levels.

Biological disorders related to insulin resistance can manifest at 4 major sites in the body, including adipose tissue, hepatic tissue, skeletal muscle tissue, and pancreatic tissue. Primary enzymes that may be adversely influenced with insulin resistance and that may contribute to insulin resistant-related disorders in adipose tissue, hepatic tissue, skeletal muscle tissue, and pancreatic tissue include hormone sensitive lipase (HSL), lipoprotein lipase (LPL), lecithin cholesterol acyltransferase (LCAT), hepatic lipase (HL), and cholesterol ester transfer protein (CETP). A brief review describing how HSL, LPL, LCAT, HL, and CETP normally functions will follow so that the adverse effects that insulin resistance may have on the primary enzymes, and ultimately on circulating TG and HDL-C levels, may be more easily understood throughout the text.

Hormone Sensitive Lipase

HSL is located in adipocytes (fat cells) and skeletal muscle cells, and is responsible for catalyzing lipolysis (breakdown) of stored fat (in the form of TG) into glycerol and three FFA which are the basic structural components of the TG molecule. FFA released by HSL-induced lipolysis of TG have a number of different fates. For instance, FFA may be oxidized for energy by the cells in which they were generated (11,43), FFA may be released into the bloodstream to circulate to other tissues of the body (11,43), and FFA may recombine with alpha glycerolphosphate (a substrate formed during glucose metabolism) to reform TG in adipocytes and skeletal muscle cells (11,43). FFA released into the bloodstream from abdominal adipocytes travel directly to the liver and increase the liver's production of TG-rich very low-density lipoproteins (VLDL), the main transport vehicle for TG during fasting conditions. By contrast, glycerol's only fate is to be released into the bloodstream. Thus, the presence of glycerol in the bloodstream is frequently used to determine the rate of lipolytic activity (11,43). Furthermore, it is important to understand that glycerol must first be phosphorylated to alpha glycerolphosphate by glycerol kinase in the liver before it can recombine with FFA to form TG in adipocytes and skeletal muscle cells (11,43).

The primary hormonal mediators of HSL include the catecholamines, norepinephrine and epinephrine (11). Binding of norepinephrine and epinephrine to beta adrenergic receptors on adipocytes and skeletal muscle cells stimulate HSL and lipolysis, whereas binding of norepinephrine and epinephrine to alpha adrenergic receptors on adipocytes and skeletal muscle cells inhibit HSL and lipolysis (11,43). Thyroid hormones and androgens (male sex hormones) increase lipolysis by increasing the number of beta adrenergic receptors (11). Thus, the increase in beta adrenergic receptors by androgen and thyroid hormonal activity further increases the potential for catecholamines to bind to the beta adrenergic receptors and stimulate lipolysis. Growth hormone increases lipolysis by stimulating the synthesis of HSL (11). By contrast, insulin inhibits lipolysis by decreasing the number of beta adrenergic receptors and by stimulating phosphodiesterase which inhibits the activity of HSL (43). Thus, insulin

resistance results in a loss of insulin-mediated suppression of HSL and, therefore, contributes to a greater rate of lipolysis and plasma FFA.

Lipoprotein Lipase

LPL is an enzyme bound to the endothelial capillary lining of the heart, skeletal muscle, and adipose tissue, and is responsible for hydrolysis of the TG core of chylomicrons (i.e., the main transport vehicle for TG in the fed state) and very low-density lipoprotein (VLDL) particles (10,41). Each TG molecule is hydrolyzed by LPL into glycerol and three fatty acids, which may be removed from the circulation by target tissues and used for either energy production or energy storage (31,37,41). Chylomicron and VLDL remnants are formed after repeated LPL-mediated hydrolysis of the TG core of chylomicrons and VLDL particles, and are removed from the circulation by the liver by hepatic apoB/E receptor recognition of apolipoprotein E[1] lying on the surface of the circulating chylomicron and VLDL remnants (31,37,41).

LPL is also involved in the formation of mature HDL_3 particles. HDL_3 particles are formed when phospholipids and apolipoproteins are transferred from TG-rich chylomicrons and VLDL particles to nascent HDL_3 particles during LPL-mediated hydrolysis of the TG core of chylomicrons and VLDL particles (31,37,41,118). Thus, increases in LPL activity ultimately lower circulating levels of TG and raise circulating levels of HDL-C.

Insulin stimulates LPL to hydrolyze TG into glycerol and three fatty acids (7,43). Furthermore, by increasing glucose uptake into adipocytes and skeletal muscle cells and by increasing the availability and uptake of FFA by stimulating LPL, insulin promotes the reformation, or reesterification, of stored TG within adipocytes and skeletal muscle cells (11,43). Because insulin stimulates LPL, LPL may become increasingly less active as insulin resistance worsens. The insulin resistant-related reduction in LPL activity contributes to higher circulating levels of TG-rich chylomicrons and VLDL particles (7,41), and lower circulating levels of HDL-C (41). Furthermore, chylomicron remnants

[1] Apoliproteins lie on the surface of lipoprotein molecules and serve as recognition sites for cell receptors on target tissues and as enzyme activators and enzyme inhibitors (9,35,104).

being removed by the liver may contain greater amounts of TG which may further promote VLDL production.

Lecithin Cholesterol Acyltransferase

LCAT is an enzyme responsible for the formation of HDL_2 from HDL_3 (31,41,118). Although HDL_3 and HDL_2 work together to remove cholesterol from the artery walls, high levels of HDL_2-C are most consistently associated with lower CHD risk (31,118). LCAT lies on the surface of HDL_3 and promotes the esterification of cholesterol with a fatty acid transferred from lecithin following HDL_3-mediated removal of nonesterified cholesterol from peripheral tissues. LCAT is responsible for the translocation of esterified cholesterol to the core of HDL_3. The accumulation of esterified cholesterol within the HDL_3 core by repeated LCAT activity shifts the dense HDL_3 particle to the less dense, antiatherogenic HDL_2 particle (31,41,118).

Although the influence that insulin resistance may have on cholesterol efflux or LCAT activity is not known, it is possible that an insulin resistance-related defect in LCAT activity may contribute to reductions in circulating HDL_2-C. Some evidence suggests that apolipoprotein A-1 catabolism increases as insulin resistance worsens (41,98). Because apolipoprotein A-1 activates LCAT, an insulin resistant-related increase in apolipoprotein A-1 catabolism would reduce LCAT activity and subsequent HDL_2-C formation.

Hepatic Lipase

HL is an enzyme bound to the endothelial lining of hepatic tissue and is responsible for either complete degradation of HDL_2 into bile acids, or partial removal of cholesterol from HDL_2 and reformation of HDL_3, which is then released back into the circulation (31,118,122). Apolipoprotein A-1 is lost when HDL_3 is reformed from HDL_2 by HL (31,118), which may reduce LCAT activity and HDL_2 formation. Thus, an increase in HL activity may contribute to lower circulating levels of HDL-C. Some

evidence suggests that greater HL activity is associated with lower HDL_2-C in NIDDM (41).

Androgens and estrogens (female sex hormones) have opposing influences on HL activity and HDL synthesis (122). Androgens are associated with increases in HL activity and lower levels of circulating HDL_2-C, and estrogens are associated with reduced HL activity and higher levels of circulating HDL_2-C (1122). However, older men with reduced androgenic activity have low HDL-C levels (7). Therefore, the associations between androgenic activity and HDL-C levels are not always consistent. It is possible that age-related increases in abdominal fat which frequently accompany age-related reductions in androgenic activity in men (7) may contribute to lower circulating levels of HDL-C in older men. In this regard, lower HDL-C levels are associated with greater amounts of visceral (intra-abdominal) fat in men of varying age (17). Furthermore, increases in visceral fat are associated with increases in HL activity in premenopausal women (21,22,24), such that premenopausal women with more visceral fat have greater HL activity and lower HDL_2-C levels relative to premenopausal women with less visceral fat, but similar amounts of total fat (22). Possible mechanisms explaining the relationship between increases in visceral fat and increases in HL activity and lower HDL-C levels will be revisited later in the text.

Although the mechanisms underlying the regulation of sex hormones by HL activity and HDL-C synthesis are not well-understood, possible regulatory sites by which sex hormones may influence HL synthesis and HL activity include 1). Transcription of HL in hepatic tissue, 2). Post-translational modification of HL in hepatic tissue, 3). Secretion of HL into the circulation, 4). Transport of HL from hepatic tissue to endothelial tissue, and 5). Binding of HL to hepatic endothelial cells (122).

Cholesterol Ester Transfer Protein

CETP catalyzes the transfer of TG from chylomicron and VLDL remnants to HDL_2 particles and the transfer of esterified cholesterol from the core of HDL_2 particles to chylomicron and VLDL remnants (24,31,41,98,118). Insulin resistant-related increases in circulating levels of TG stimulate CETP (31,41,96,98,118). CETP-mediated

accumulation of TG within HDL_2 particles may increase the susceptibility of HDL_2 to hydrolysis by HL, thus lowering circulating levels of HDL-C (24,31,41,98,118,122). In fact, the majority of evidence suggests that insulin resistant-related reductions in circulating HDL-C levels are primarily mediated by increases in CETP activity (24,41,98).

In summary, insulin resistant-related increases in the activities of HSL, CETP, and HL, and reductions in the activity of LPL, ultimately contribute to high circulating levels of TG and low circulating levels of HDL-C. The loss of insulin's inhibitory influence on HSL with insulin resistance leads to increases in HSL activity, which in turn, increases lipolysis, hepatic FFA flux, and VLDL production. An insulin-related reduction in LPL activity reduces chylomicron and VLDL hydrolysis, which increases circulating levels of chylomicrons and VLDL, and reduces circulating levels of HDL-C. Again, chylomicrons are the main transporters for TG in the fed state and VLDL are the main transporters for TG in the fasting state. Thus, an increase in circulating levels of chylomicrons and VLDL is representative of an increase in circulating TG levels. Furthermore, increases in circulating TG levels stimulate CETP and the accumulation of TG in HDL_2, which in turn, increases the susceptibility of HDL_2 to hydrolysis by HL, thereby lowering circulating HDL-C levels. Therefore, high plasma TG levels and low plasma HDL-C levels are believed to result from unfavorable alterations in enzymatic activity which are mediated, in large part, by an increase in insulin resistance.

The cause of insulin resistance in humans is controversial. Abdominal fat is strongly associated with insulin resistance and its associated CHD metabolic risk factors (21,24,26,35,45,65,92), and may proceed the onset of the insulin resistant CHD risk factors (21,24). However, because studies examining the association between insulin resistance and abdominal obesity frequently include human subjects which are already insulin resistant and obese, it is difficult to determine the primary cause of insulin resistance. The majority of evidence suggests that age-related increases in abdominal fat largely account for the age-related increases in insulin resistance (16,45,63,106). In this regard, high dietary fat intake, caloric intake in excess of caloric output, age-related changes in circulating sex hormones, and age-related reductions in physical activity largely account for abdominal fat accumulation (21). Increases in lipolytic activity of

abdominal fat cells contribute to high levels of plasma FFA, which may be the initial metabolic disorder contributing to the manifestation of insulin resistant CHD risk factors (21,24,45). Greater amounts of abdominal fat in men and women are consistently associated with insulin resistant CHD risk factors, including higher fasting insulin (35,106) and fasting glucose (65) levels, higher insulin (35,92,106) and glucose (35,65,92,106) responses to an oral glucose load, higher steady state plasma glucose levels during a hyperinsulinemic, euglycemic clamp (63) and during a hyperglycemic clamp (61), and higher circulating levels of TG (13,25) and lower circulating levels of HDL-C (13,17,25).

Visceral fat gain is believed to be the primary determinant in abdominal fat-related increases in insulin resistance. Visceral obesity is characterized by large adipocytes which are more resistant to insulin action (35), possibly resulting from a low insulin receptor density in visceral fat and/or a postreceptor defect (i.e., a defect in insulin's ability to suppress HSL activity)(7). Because visceral adipocytes are more resistant to insulin, insulin-mediated suppression of lipolysis in visceral adipocytes is reduced, which markedly increases the rate of lipolysis and FFA flux to the liver (41,96). The increase in hepatic FFA flux inhibits the liver from extracting insulin from the circulation (41,96), thereby contributing to a deterioration in insulin sensitivity, an increase in plasma insulin levels, and insulin resistance.

FFA-mediated reductions in hepatic insulin extraction and increases in hepatic fat oxidation markedly increase plasma glucose levels by reducing hepatic glucose uptake and increasing hepatic glucose production (96,124). Reductions in hepatic insulin extraction may reduce hepatic glucose uptake and contribute to high concentrations of plasma glucose by indirectly reducing GLUT 2-mediated transport of glucose into hepatocytes (liver cells). Although the GLUT 2 transport protein in hepatocytes is not directly dependent on insulin for its essential role in transporting glucose across hepatic cell membranes, GLUT 2 is highly dependent on the glucose concentration gradient between plasma and hepatocytes, which is directly influenced by insulin. High plasma glucose concentrations relative to hepatic intracellular glucose concentrations will favor GLUT 2-mediated transport of glucose from the plasma into hepatocytes. By contrast, high hepatic intracellular glucose concentrations relative to plasma glucose

concentrations will favor GLUT 2-mediated transport of glucose from hepatocytes into the plasma. Insulin stimulates glucokinase, a key enzyme in hepatocytes responsible for the irreversible phosphorylation of glucose to glucose 6-phosphate during glucose metabolism. The formation of glucose 6-phosphate by glucokinase reduces intracellular glucose concentrations and, therefore, favors GLUT 2-mediated transport of glucose into hepatocytes from the plasma, which in turn, lowers concentrations of plasma glucose. Because a FFA-related impairment in hepatic insulin extraction reduces glucokinase activity in hepatocytes, intracellular hepatic concentrations of glucose remain high, which favors GLUT 2-mediated transport of glucose into the plasma from hepatocytes and higher concentrations of plasma glucose.

Under normal conditions, insulin acts to inhibit glucose 6-phosphatase, an enzyme unique to hepatocytes (and kidney cells) and responsible for converting glucose 6-phosphate to glucose during the reactions of gluconeogenesis, a metabolic process which synthesizes glucose from noncarbohydrate sources such as lactate, amino acids, and glycerol. (11,43). Reductions in hepatic insulin extraction secondary to hepatic FFA flux removes the inhibition on glucose 6-phosphatase and, therefore, contributes to increases in gluconeogenesis, hepatic glucose production, and plasma glucose levels (124).

An increase in hepatic fatty acid oxidation increases concentrations of acetyl-CoA (a metabolic end product of fatty acid oxidation), which reduces glucose uptake and metabolism by the liver, and increases hepatic glucose output and plasma glucose levels (96,98). More specifically, high concentrations of acetyl CoA inhibit pyruvate dehydrogenase activity, a key enzyme responsible for converting pyruvate to acetyl CoA during glucose metabolism. Reductions in pyruvate dehydrogenase inhibit glucose uptake and metabolism. In addition, high concentrations of acetyl CoA stimulate the activity of pyruvate carboxylase, a key enzyme responsible for converting pyruvate to oxaloacetate during gluconeogenesis. By inhibiting pyruvate dehydrogenase and stimulating pyruvate carboxylase, fatty acid oxidation-related increases in acetyl CoA are linked to reductions in hepatic glucose uptake and increases in hepatic glucose output. Thus, reductions in hepatic glucose uptake and increases in hepatic glucose output substantially contribute to higher plasma glucose levels.

It is important to understand that under fasting conditions, noninsulin-dependent tissues, such as the brain, constitute the major sites of glucose uptake (124). Therefore, reductions in glucose uptake into insulin-dependent tissues contribute little to high fasting blood glucose levels. Rather, the primary defect contributing to high fasting blood glucose levels is believed to result from insulin's inability to effectively suppress hepatic glucose production (98,124). However, hepatic glucose production is frequently overestimated in individuals with high fasting glucose levels due to the inaccurate, widespread use of calculations to compensate for an expanded glucose pool and the resulting absence of steady state conditions when using isotopic techniques (98). When more specific tracer techniques are used, which are not confounded by a large glucose pool, hepatic glucose production is approximately 30% higher than normal in individuals with very high levels of fasting glucose. Thus, other factors must contribute to high fasting glucose levels in addition to increases in hepatic glucose production (98). For instance, it is possible that abnormally high circulating levels of FFA may impair noninsulin-dependent glucose uptake, which would contribute to higher blood glucose levels during fasting.

Insulin resistant-related increases in potentially atherogenic VLDL particles are mediated by a number of possible and additive mechanisms, including increases in FFA hepatic uptake, reductions in LPL activity, and high blood glucose-mediated glycosylation of chylomicron and VLDL remnants. For instance, excessively high delivery of FFA to the liver, secondary to higher rates of lipolysis in abdominal adipocytes and higher plasma FFA levels, become the major precursors for endogenous VLDL-TG synthesis and secretion (21,24). Furthermore, because insulin is a potent stimulator to LPL, insulin resistant-related reductions in LPL activity also contribute to higher circulating levels of VLDL particles and chylomicrons (7,41). Chylomicron remnants removed from the circulation by the liver may contain greater amounts of TG which may further promote VLDL production. It is also possible that abnormally high blood glucose levels accompanying severe insulin resistance may increase the susceptibility of chylomicron and VLDL remnants to glycosylation (i.e., nonenzymatic attachment of glucose), which in turn, may impair hepatic removal of chylomicron and VLDL remnants (41).

Insulin resistance is characterized by a deterioration in insulin sensitivity in skeletal muscle and a reduction in insulin-mediated glucose disposal into skeletal muscle (96,98,124). Because the GLUT 4 transport protein in skeletal muscle is directly dependent on insulin for its action, a reduction in skeletal muscle glucose uptake with insulin resistance most likely results in an impairment in GLUT 4-mediated transport of glucose into skeletal muscle cells (124). More specifically, the binding of insulin to its receptor on the skeletal muscle cell membrane surface stimulates the insulin signalling pathway and the ultimate translocation of the GLUT 4 transport protein from its intracellular location to the skeletal muscle cell membrane (11,43). The transport and attachment of GLUT 4 to the skeletal muscle membrane is necessary for its essential role in transporting circulating glucose into skeletal muscle (11,43). Because insulin resistance (44) and NIDDM (124) are not associated with low GLUT 4 concentrations, the primary defect responsible for an insulin resistant-related reduction in skeletal muscle removal of glucose is believed to result from a defect in the insulin signalling pathway and the transport of GLUT 4 to the skeletal muscle membrane (43,124).

The possible mechanisms responsible for insulin resistant-related impairments in GLUT 4 translocation are controversial (44,99,124). One possible explanation accounting for the defect in insulin signalling and GLUT 4 translocation with insulin resistance may be the increase in plasma FFA concentrations and skeletal muscle fatty acid oxidation secondary to increases in visceral adipocyte lipolysis and/or high intake of dietary fat. Some evidence suggests that fatty acid oxidation-related increases in acetyl CoA and reductions in pyruvate dehydrogenase activity (i.e., described previously with respect to hepatic cells) within muscle cells inhibit glucose metabolism and glucose transport into skeletal muscle cells via the glucose-fatty acid cycle (95). The theory behind the glucose-fatty acid cycle suggests that the availability of fatty acids determines the rate of fatty acid metabolism in the skeletal muscle, and that increases skeletal muscle fatty acid oxidation inhibits the uptake and oxidation of glucose by skeletal muscle by interfering with the insulin signalling pathway (95). In this regard, it is hypothesized that high TG content in skeletal muscle cells, in response to high fat feeding, favors fat oxidation, which, in turn, inhibits glucose uptake and metabolism via fatty acid oxidation-related increases in acetyl CoA. In fact, insulin resistance (44,79)

and visceral fat (44) gain are evident in rats after only 4 weeks of high fat feeding. In addition, high fat intake-induced insulin resistance and visceral fat gain can worsen and progress into severe visceral obesity, severe hyperinsulinemia, severe hyperglycemia, and over time, NIDDM (44).

In summary, increases in circulating levels of FFA impair glucose uptake into hepatic and peripheral tissues, increase hepatic glucose production, increase hepatic production of TG-rich VLDL, increase hepatic degradation of HDL-C by HL, and inhibit pancreatic secretion of insulin (98). Furthermore, chronically high circulating plasma FFA concentrations inhibit LPL activity which reduces the formation of HDL and further contributes to high plasma TG levels. Thus, abdominal fat-related increases in plasma FFA concentrations are believed to be largely responsible for insulin resistance-related impairments in glucose metabolism and atherogenic alterations in circulating TG and HDL-C levels, which in turn, profoundly increase the risk for NIDDM and CHD.

The Influence of Physical Activity on Insulin Resistance and Circulating Levels of TG and HDL-C

Approximately 12% of all deaths in the United States each year are related to physically inactive, sedentary lifestyles (82). It is estimated that 29.2% of American adults participate in no leisure-time physical activity, and 43.1% of American adults do not participate in enough leisure-time physical activity to obtain any meaningful health benefits (93). Furthermore, men participate in physical activity more frequently than women (82,93), and participation in physical activity declines with age (65).

The risk for developing NIDDM and CHD increases with age, obesity, and lack of physical activity (82,100). Physical activity is know to reduce the risk for NIDDM and CHD by improving insulin resistant CHD risk factors including TG and HDL-C levels, blood pressure, body composition, insulin sensitivity, and glucose tolerance (82,123,124). In fact, physically inactive individuals are 1.5 to 2.4 times more likely to develop CHD relative to their active counterparts (82).

Physical activity favorably influences insulin/glucose homeostasis by improving insulin sensitivity and insulin action, primarily in skeletal muscle, which in turn, reduces insulin secretion from the beta cell (i.e., insulin response) and circulating insulin levels (27,61,82,124). For instance, Kirwan et al. (61) observed significantly lower fasting insulin levels, significantly less insulin secretion to an oral glucose load, and significantly less insulin secretion during a hyperglycemic clamp without a change in glucose disposal rate following 9 months of exercise training in elderly adults. The lower insulin response without a change in glucose disposal rate suggests an increase in insulin sensitivity in skeletal muscle (i.e., improved insulin resistance) with exercise training. Therefore, a similar amount of glucose was infused before and after training, but a lower insulin response to the infused glucose was observed following training, thereby demonstrating the effect that exercise can have on reversing the age-related reductions in insulin sensitivity and glucose tolerance.

An increase in the concentration of the GLUT 4 transport protein is believed to be primarily responsible for the increase in insulin sensitivity and improved insulin resistance associated with physical activity (53,124). Contraction-mediated glucose

uptake is also enhanced by increases GLUT 4 concentration with exercise (11). GLUT 4 expression in rat skeletal muscle increases rapidly following the onset of exercise (99). However, the exercise-related increase in GLUT 4 concentration and insulin sensitivity is transient and, if exercise is not repeated, returns to baseline within 40 hours following an acute exercise bout (50). Thus, regular, consistent participation is necessary to maintain improvements in insulin sensitivity. The increase in GLUT 4 concentration and insulin sensitivity within the hours following an exercise bout is associated with a replenishment of glycogen stores (99).

Although increases in insulin physical activity with exercise is primarily attributed to increases in the concentration of GLUT 4, other mechanisms including reduced insulin secretion from the beta cell, increased capillary density, improved insulin-receptor binding and insulin signalling, and GLUT 4 translocation are also likely to contribute to increases in insulin sensitivity and improved glucose tolerance with exercise training (53,124).

An improvement in insulin sensitivity with physical activity contributes to reductions in circulating levels of TG and elevations in circulating levels of HDL-C by its involvement in reactions which stimulate LPL activity and inhibit HSL, CETP, and HL activities. Based on the mechanisms previously described in the previous section of the literature review, insulin-mediated increases in LPL activity would lower circulating levels of TG and raise circulating levels of HDL-C; insulin-related reductions in CETP and HL activities would reduce HDL degradation, and therefore, contribute to higher circulating levels of HDL-C; and insulin-mediated suppression of HSL would reduce the FFA flux to the liver, thereby reducing VLDL production and circulating TG levels.

Manipulation of lipoproteins is the primary means for treating and preventing CHD (36). The National Cholesterol Education Program (NCEP) (36) and the American Heart Association (AHA) (39,109) recommend altering lipoprotein levels through diet modification and physical activity as the first line of treatment for primary prevention of CHD in persons who are not otherwise considered to be at risk for CHD. Physical activity is associated with lower circulating TG levels and higher circulating HDL-C levels, specifically levels of HDL_2-C (31,36,82). Consistent with findings reporting a transient increase in insulin sensitivity following acute exercise, elevations in levels of

HDL-C (4,19,56,104) and reductions in levels of TG (19) are observed immediately following or in the first few days that follow an exercise bout. If exercise is not repeated, a considerable amount of these favorable metabolic changes are lost within 48-72 hours post exercise (19). Therefore, timing of blood measurements following the last exercise session is an important consideration, and discrepancies in findings across studies with respect to metabolic changes accompanying physical activity may, in part, result from differences in the timing of blood samples.

Recent evidence suggests that nonvigorous, low to moderate intensity exercise contributes to health-related benefits comparable to those that may be achieved with higher intensity exercise when controlling for caloric expenditure (29,51,69,82). Although some evidence suggests that elevations in plasma levels of HDL-C are associated with increases in the level of exercise intensity (112), it is possible that the higher energy expenditure (i.e., volume of exercise completed) associated with higher exercise intensity, is responsible for the elevations in HDL-C levels, independent from the intensity level. For instance, when controlling for energy expenditure by having lower-intensity exercisers walk for a longer period of time than high-intensity walkers, Duncan et al. (29) observed that high-intensity walkers and low-intensity walkers had a comparable rise in HDL-C levels despite an increase in aerobic capacity among the high-intensity exercisers. Therefore, a disassociation was observed between physical fitness (aerobic capacity) and health-related benefits (HDL-C levels). Similarly, comparable improvements in insulin sensitivity are observed between vigorously active and moderately active men and women when energy expenditures are equivalent (51).

Findings from King et al. (60) further support the benefits that can be achieved with low-intensity exercise in that significant increases in HDL-C were observed in older adults following two years of participation in either a low-intensity or high-intensity home based exercise program, with no significant differences in the magnitude of HDL-C increase from baseline between the exercise interventions. Furthermore, over 50% of the low-intensity exercisers achieved elevations in HDL-C levels greater than 5 mg/dL, whereas only 30 to 35% of the high-intensity exercisers achieved elevations in HDL-C levels greater than 5 mg/dL.

Recent evidence also suggests that accumulation of short bouts of physical activity can contribute to health-related benefits comparable to a single bout of physical activity of longer duration. For instance, low-intensity exercisers in the King et al. Study (60) participated in more frequent, shorter bouts of exercise, while high-intensity exercisers participated in less frequent, longer bouts of exercise, yet improvements in HDL-C levels were most evident in the low-intensity exercisers. Ebisu et al. (34) suggest that three bouts of exercise each day significantly increase HDL-C levels relative to baseline. By contrast, one or two bouts of exercise each day of equivalent total exercise duration as that achieved with the three bouts of exercise per day did not significantly raise HDL-C levels from baseline (34). Angelopoulos et al. (4) observed HDL-C levels to be significantly higher following one, two, or three acute bouts of exercise relative baseline HDL-C levels, yet three bouts of exercise resulted in a higher and clinically significant rise in HDL-C levels from baseline relative to 1 or 2 bouts of exercise each day. Furthermore, when examining the health benefits obtained between subjects incorporating intermittent bouts of moderate-intensity physical activity accumulating at least 30 minutes each day into their daily schedules and subjects following a more structured exercise program, favorable changes in weight (54), body fat (2,30,54), waist circumference (54), blood pressure (30), total cholesterol levels (2,30), and TG levels (2) were observed following both interventions, with no appreciable differences in any of these outcomes between the exercise interventions.

Evidence demonstrating the health-related benefits achieved with consistent and frequent participation in nonvigorous, moderate-intensity physical activity have provided the underlying rationale for the current national guidelines for physical activity endorsed by the U.S. Surgeon General (123), the Centers for Disease Control and Prevention (82), and the American Heart Association (109). The current physical activity guidelines recommend a broad range of physical activity (i.e., gardening, housework, etc...) and encourage adults to accumulate at least 30 minutes of moderate-intensity activity each day which can be achieved by either one 30-minute continuous bout or by a number of short bouts of activity spread throughout the day (82,123). Current guidelines emphasize physical activity rather than exercise and physical fitness, and are aimed primarily at those persons who are most inactive since the have the most to gain from a

public health perspective (47,82). By decreasing the intensity and increasing the frequency and diversity of activity, the recommendations are more palatable for and attainable by the general public. In fact, 250,000 deaths each year in the United States may be eliminated if all Americans followed the current physical activity guidelines (82).

It is undetermined whether the favorable changes in insulin sensitivity, plasma TG levels, and plasma HDL-C levels which frequently accompany physical activity are independent from physical activity-induced body weight and body fat loss. Favorable increases in insulin sensitivity (27,61) and plasma HDL-C levels (29,132,133,134), and favorable reductions in plasma TG levels (132,133) with physical activity are frequently associated with favorable body compositional changes including reductions in body weight, body fat, and abdominal fat, but not always (112,120,126). Again, age-related increases in abdominal fat are believed to substantially contribute to the onset of insulin resistant-CHD risk factors (21,24). Because reductions in physical activity frequently accompany aging, consistent participation in physical activity may, perhaps, prevent some of the age-related increases in abdominal obesity and its associated hormonal and metabolic disturbances.

Several cross-sectional studies have observed that leaner, physically active individuals have more favorable lipid and lipoprotein levels than their heavier, inactive age-matched counterparts (32,48,128,131). An association between body composition changes and favorable alterations in selected lipid and lipoprotein levels is frequently observed following chronic exercise training (27,29,132,133,134). For example, Duncan et al. (29) identified women with the greatest reduction in body fat to have the greatest rise in HDL-C levels when combining women from all intensity-intervention groups following a 6-month training period.

The first Stanford Weight Control Project (133) was designed to address the influence of weight loss on levels of HDL-C. Weight loss occurred in both men who dieted (caloric-restricted diet) and men who exercised compared with controls, but the men who dieted were able to achieve more weight loss compared with the men who exercised. Significant reductions in TG levels in the dieters and exercisers were also observed and were significantly associated with reductions in weight. Although the men who dieted lost more weight than the men who exercised, both groups elevated their

HDL-C and HDL_2-C levels similarly following the one-year intervention. The rise in HDL-C levels was significantly related to reductions in fat and weight loss in both men who dieted and men who exercised. Therefore, elevations in HDL-C levels in the diet-induced weight loss group supports the argument that weight loss, whether accomplished by diet or exercise, is necessary to raise HDL-C levels. Furthermore, Williams et al. (130) observed that the association between distance run and elevations in HDL_2-C was no longer significant after adjusting for BMI, and Williams et al. (129) observed that elevations in HDL_2-C levels in subjects exercising in combination with a low-fat diet were no longer significant after adjusting for BMI or losses in body weight. Still, the observation that men who exercised lost less weight than the men who dieted in the first Stanford Weight Control Project (133), yet had a similar rise in HDL-C levels, supports the argument that some other component exists, independent of weight loss, that is contributing to the elevations in HDL-C levels in the men who exercised.

Favorable changes in the activities of the lipoprotein enzymes are frequently observed in the presence of weight loss (27,107,111). Significantly greater postheparin LPL activity and significantly reduced HL activity are observed in leaner male runners when compared with sedentary controls (48). Significant reductions in HL activity and increases in LPL activity following exercise-induced weight loss are observed in obese premenopausal women (27) and older men and women (107). Moreover, LPL activity is increased and hepatic lipase activity is reduced when weight loss is achieved by either diet or exercise (111).

By contrast, a number of studies have demonstrated that favorable CHD risk-reducing elevations in HDL-C levels (112,120) and LPL activity (126), and CHD risk-reducing reductions in TG levels (126) and CETP activity (107) may occur without a concomitant loss in weight. Significantly higher levels of HDL-C are observed in physically active men and postmenopausal women aged 50-89 years and significantly reduced levels of TG are observed in physically active men aged 50-89 years compared with their inactive counterparts after adjusting for either BMI or the WHR (97). Furthermore, significant rises in levels of HDL-C are observed in men exercising at 75% and 85% of their aerobic capacity relative to inactive controls (112), and in men

following 15 weeks of moderate-intensity training (83), without a loss in either body weight or body fat.

Evidence from the second Stanford Weight Control Project (134) and the Diet and Exercise for Elevated Risk (DEER) study (110) suggest that elevations in levels of HDL-C with exercise cannot be exclusively mediated by weight loss. In contrast to the caloric restricted-induced weight loss diet in the first Stanford Weight Control Project, the diet in the second Stanford Weight Control Project restricted calories by restricting dietary fat in an attempt to more effectively lower LDL-C levels in overweight men and premenopausal women. Although men who dieted, but did not exercise, lost significant amounts of body fat and weight with the fat-restricted diet relative to controls, they were unable to achieve the rise in HDL-C levels previously observed in men who lost weight by reducing caloric intake in the first Stanford Weight Control Project. Furthermore, the restriction of dietary intake of fat offset the favorable rise in HDL-C levels observed with a caloric-restricted, but not fat-restricted weight loss diet.

Men who dieted and exercised in the second Stanford Weight Control Project lost significantly more weight and fat, and achieved significant elevations in HDL-C levels and significant reductions in TG levels relative to men who dieted (fat-restricted), but did not exercise, and controls. However, it is unclear whether the significant rise in HDL-C observed in men who dieted and exercised was obtained by the exercise or by the additional weight loss that occurred in men who dieted and exercised.

Weight loss was similar between women who dieted and exercised and women who dieted, but did not exercise, in the second Stanford Weight Control Project (134). However, the fat-restricted diet lowered HDL-C levels in the women who dieted, but did not exercise, compared with women who dieted and exercised, and women controls. Moreover, despite the influence of weight loss and exercise, women who dieted and exercised were unable to raise their HDL-C levels in the presence of the low-fat diet. Similarly, Beard et al. (6) observed reductions in levels of HDL-C in men and women, despite weight loss, following exercise in combination with a very low-fat diet regime. Thus, elevations in HDL-C levels cannot be completely mediated by weight loss.

One possible mechanism explaining the lower levels of HDL-C observed with low fat diets may be that less cholesterol, phospholipid, and apolipoproteins from

circulating chylomicrons are available to be transferred to HDL with low fat diets (77). Beard et al. (6) argue that low levels of HDL-C associated with low fat diets do not have the same prognostic implications as do low levels of HDL-C associated with the typical American diet. Although the NCEP (36) and the AHA (109) consider low levels of HDL-C to be associated with increased risk, the Tarahumara Indians consume very little fat and have HDL-C levels below the minimum advised levels established by the NCEP, yet the presence of CHD is extremely rare in this population (71). Still, a fat-restricted diet may not be appropriate for persons with initially low levels of HDL-C. Nevertheless, the inclusion of an appropriate dietary analysis across studies is necessary to consider how potential dietary differences among study participants may confound the interpretations regarding the influence of exercise and weight loss on circulating levels of lipoproteins.

Findings from the DEER study (110) support the hypothesis that exercise may raise levels of HDL-C, independent from weight loss, and further support the hypothesis that fat-restricted diets lower levels of plasma HDL-C. In this regard, no significant elevations in levels of HDL-C were observed in either men or postmenopausal women with low baseline HDL-C levels who dieted (fat-restricted), but did not exercise, or in men and postmenopausal women with low baseline levels of HDL-C who dieted (fat-restricted) and exercised, despite similar and significant weight loss in both groups. However, HDL-C levels tended to be higher in men and postmenopausal women who exercised, but did not diet, even though weight loss was not achieved in either group.

Thompson (120) suggests that discrepancies across studies with respect to the influence that weight loss has on HDL-C levels may, in part, be attributed to plasma volume changes that have not been considered following the intervention period. More specifically, reductions in plasma volume that accompany dietary-induced weight loss may lead to an overestimation of HDL-C levels. By contrast, plasma volume expands following a chronic exercise training program and may lead to an underestimation of elevations in HDL-C levels. Thus, a comparison between the effects of exercise with and without weight loss on plasma volume needs to be addressed to better understand how plasma volume changes may confound possible interpretations regarding the influence that exercise and weight loss have on circulating levels of HDL-C.

Elevations in HDL-C levels and reductions in TG levels following exercise training, independent from weight loss, may result from local adaptations occurring at the level of the skeletal muscle (59,67). Cross-sectionally, Nikkila et al. (78) observed significantly higher levels of skeletal muscle LPL activity in male and female long distance runners relative to their less active counterparts having the same body weight. Furthermore, a significant increase in mean skeletal muscle LPL activity was observed in 6 Swedish elite soldiers on heavy work days relative to inactive control days, and was related to urinary epinephrine excretion (67). Because epinephrine stimulates lipolysis, increases in circulating epinephrine levels with physical work may indirectly stimulate LPL to replace skeletal muscle TG stores lost with the exercise. Kiens and Lithell (59) observed mean skeletal muscle LPL activity to be 70% higher in trained legs relative to untrained legs following a well-controlled 8-week one-legged training intervention. The rise in skeletal muscle LPL activity in the trained legs was related to arteriovenous differences in HDL-C and HDL_2-C, and inversely related to arteriovenous differences in VLDL-TG. In addition, the exercise-induced increases in skeletal muscle LPL activity were associated with exercise-induced increases in capillary density, which in turn, may create more binding sites for LPL.

Although controversy still exists regarding whether favorable changes in insulin sensitivity, TG levels, and HDL-C levels with physical activity are independent from physical activity-induced weight loss, increases in insulin sensitivity (50) and HDL-C levels (4,19,56,104), and reductions in TG levels (19) are observed immediately following, or in the first few days that follow an acute exercise bout, independent from a change in body composition. If exercise is not repeated, a considerable amount of the favorable changes in insulin sensitivity, HDL-C, and TG are lost with 48 to 72 hours following the last exercise bout (19,56). Therefore, it is possible that favorable changes in insulin resistant CHD risk factors are achieved by repeated acute bouts of exercise, whereas reductions in total and abdominal body fat may be more related to chronic exercise training. In turn, chronic exercise-related reductions in total and abdominal body fat may have long-term additive effects on improving the insulin resistant CHD risk factors achieved by repeated acute bouts of activity.

In summary, physical activity reduces CHD risk, in large part, by reducing total and abdominal fat, improving insulin sensitivity and insulin resistance, reducing circulating levels of TG, and raising circulating levels of HDL-C. Improvements in the insulin resistant CHD biological risk factors are mediated primarily by CHD risk-reducing alterations in metabolic enzymatic activity. Furthermore, nonvigorous, moderate physical activity can reduce CHD risk comparable to reductions in CHD risk achieved with higher intensity exercise. Thus, current physical activity recommendations, which emphasize less intense forms of physical activity, are more attainable by the general public, and may increase long-term adherence to physical activity by the general public. Moreover, because physical activity recommendations emphasize a broad range of frequent, moderate-intensity forms of physical activity, these guidelines may be attainable by persons with MS.

Physical Activity in Persons with Multiple Sclerosis

With the continual development of new medications for the treatment of MS, women with MS are likely to live full life spans. However, because physical inactivity is a major risk factor for the development of NIDDM and CHD (36,82,123), and because persons with MS are frequently more sedentary than age- and gender-matched sedentary controls (76,87,113,114), persons with MS may be at even greater risk for NIDDM and CHD with increasing age relative to their non-MS counterparts. For instance, the direct measurement of physical activity with a three dimensional accelerometer (76) and the indirect measurement of physical activity with the Health Promoting Lifestyle Profile II survey (114) identify persons with MS as being less active than age- and gender-matched controls.

Furthermore, extended or frequent periods of corticosteroid use by persons with MS raises NIDDM and CHD risk by stimulating lipolysis and proteolysis (protein breakdown). Again, lipolysis increases FFA flux to the liver which impairs hepatic insulin extraction and ultimately contributes to insulin resistance, high circulating levels of glucose, high circulating levels of TG, low circulating levels of HDL-C, and the development of NIDDM and CHD (21,96,98). Muscle proteolysis makes amino acids available to the liver for glucose synthesis through the reactions of gluconeogenesis (11). The diffusion of glucose into the bloodstream from the liver increases circulating levels of glucose which further raises the risk for developing NIDDM and CHD. Thus, regular participation in physical activity, which is known to improve insulin resistant CHD biological risk factors, may oppose the negative influence that corticosteroid use has on the insulin resistant CHD risk factors (89,114).

Although it is likely that persons with MS who adopt physically active lifestyles will achieve health-related benefits similar to the general population, several perceived barriers, including fatigue, mobility, transportation, fear, and overheating, limit the extent by which persons with MS can effectively and consistently incorporate health promotion practices into their daily lives (113,114,115). In fact, just the diagnosis of MS, independent from the clinical status and severity of MS, is suggested to be responsible for the low activity levels in persons with MS (76).

Fatigue affects the majority of persons with MS. Three types of fatigue are experienced by persons with MS (103): 1). Normal fatigue that occurs with the activities of daily living. A considerable amount of this 'normal' fatigue may be attributed to deconditioning and muscle disuse associated with low levels of physical activity, 2). Fatigue associated with impaired functioning of the CNS which is characterized by gait disturbances and limping during short periods of walking. In more severe cases, a complete block of nervous system conduction may occur causing walking to cease, and 3). Fatigue associated with disturbances in neurochemical processes which manifests as extreme sleepiness.

A rise in body in body temperature accompanying physical activity is a major concern among persons with MS (87,113). Body temperature elevations contribute to fatigue and worsen the symptoms of MS (86,87). Because water exercise may lessen body temperature elevations that frequently accompany land exercise, water exercise may be the preferred mode of physical activity for those with MS. Water exercise is perceived as less stressful by persons with MS relative to identical exercise performed on land (89). Furthermore, persons with MS report that "swimming provides a sense of self-efficacy that cannot be achieved with other activities because water provides a buoyancy that makes weak muscles feel strong (113)." When exercise must be performed on land, however, cool showers prior to exercise, light clothing, and the operation of fans during exercise may minimize heat intolerance associated with land exercise (87).

Persons with MS have lower aerobic capacities (80,89,90) and less muscular strength, power, and endurance relative to their sedentary, otherwise healthy, counterparts without MS. Less muscle strength and lower aerobic capacities in persons with MS may be attributed, in large part, to the effects of cardiovascular deconditioning and skeletal muscle structural changes associated with their low levels of physical activity (58,80,90). Ponichtera-Mulcare et al. (90) observed that aerobic capacities of persons with mild to moderate MS did not differ between maximum cycling efforts performed in the water and maximum cycling efforts performed on land. However, aerobic capacities of person with MS were lower in both exercise environments relative to sedentary controls without MS, yet perceived fatigue was similar between the two groups, and fatigue in persons with MS was not related to the symptoms of MS.

Furthermore, some persons with MS had blunted heart rates to increasing workloads (90). By contrast, Ogliati et al. (80) observed the heart rates of persons with MS to be higher than heart rates expected from standard oxygen consumption ranges. Thus, the indirect method of estimating maximum aerobic capacity from submaximum heart rate and work rate data may not be accurate for the population with MS.

Oxygen pulse (stroke volume x arteriovenous oxygen difference), the major component of aerobic capacity, is reduced in persons with MS, and may be explained by a reduction in stroke volume and/or arteriovenous oxygen difference (80). Stroke volume is the amount of blood pumped out of the heart each beat and is an index of cardiovascular functioning. Low stroke volume in persons with MS may reflect an autonomic nervous system abnormality, common in MS, causing reductions in stroke volume and increases in heart rate (80). The arteriovenous oxygen difference is the difference between the oxygen content in arterial blood and the oxygen content in mixed venous blood. The arteriovenous oxygen difference reflects the amount of oxygen extracted by the tissues and is dependent upon sufficient oxidative enzymatic activity, capillarization, and mitochondrial density and activity. Thus, the arteriovenous oxygen difference is an index of muscle functioning. Low arteriovenous oxygen difference in persons with MS reflects muscle disuse and is consistent with smaller fiber size, less slow twitch fibers (necessary for aerobic exercise), and lower succinate dehydrogenase activity (an oxidative enzyme in the KREBS cycle required for aerobic energy metabolism) in skeletal muscle observed in persons with MS relative to healthy controls (58). In addition, ventilation (80,119), breathing frequency (80,119), and the ventilatory equivalent (V_E/VO_2) (80) are observed to be higher in persons with MS. A higher ventilatory equivalent reflects greater anaerobic metabolism and less aerobic metabolism resulting from lower oxidative capacities of the muscle from disuse. More specifically, the buffering of lactic acid generated from anaerobic metabolism increases nonmetabolic carbon dioxide production which stimulates ventilation and raises the ventilatory equivalent (11).

Although several studies have identified persons with MS as being less active and less aerobically fit relative to age- and gender-matched controls without MS (76,80,90,119), only a few studies (86,108) have examined the improvements in aerobic

fitness and CHD risk factors following an exercise intervention. In this regard, increases in aerobic capacity (86,108), work capacity (86,108), and muscular strength (86), and reductions in circulating levels of TG (86) and skinfold thicknesses (86) are observed following 4 months of moderate-intensity aerobic exercise in persons with MS ranging from low to moderate disability. Furthermore, these health-related gains were observed without an increase in the incidence of exacerbations or symptoms related to MS (86,108). Shapiro et al. (108) observed that persons with more progressive MS (EDSS > 3.5) were able to significantly raise their maximum aerobic capacities, but not to the same extent as persons with milder MS (EDSS > 3.5) following a home-based endurance exercise program. By contrast, Petajan et al. (86) observed maximum aerobic capacity to be equally raised in mild and more progressed forms of MS following an endurance training intervention in a controlled, laboratory setting. Moderate reductions in plasma TG levels were reported by Petajan et al. (86), but no favorable elevations HDL-C were observed by Petajan et al. (86) or Shapiro et al. (108) following 4 months of exercise training. Thus, it is possible that persons with MS may require a longer training period to raise plasma HDL-C levels. Moreover, no studies have measured changes in fasting insulin levels or changes in insulin responses to an oral glucose load in persons with MS following participation in an exercise program. Clearly, more research is needed to address the effect that physical activity may have on improving the insulin resistant CHD risk factor profile in the MS population.

Although the symptoms of MS may require modification in the mode, frequency, and duration of physical activity, it is clear that persons with MS are capable of participating in and achieving health-related benefits associated with physical activity. Adherence to the exercise intervention imposed in training studies is high in subjects with MS (86), which reflects their desire to improve physical fitness and functioning when appropriate information and guidance is provided regarding how to exercise safely given the limitations associated with MS. Gains in aerobic fitness following exercise training can significantly improve mobility and the ability to perform activities of daily living, which in turn, reduces the extent of 'normal' fatigue experienced in persons with MS (86). By improving mobility (86) and the quality of life, and by lessening fatigue (86) in persons with MS (89,114), physical activity may, perhaps, reduce the high incidence of

depression and suicide among persons with MS (86,103,105). In fact, women with MS regard physical activity as an essential component for "coping with the physical demands of the illness (113)."

Thus, it is essential that physical activity recommendations are developed specifically for persons with MS to overcome potential barriers prohibiting participation in physical activity, and to reduce the development of physical inactivity-related medical problems. In this regard, the United States Surgeon General emphasizes the need for research addressing preventative measures for reducing CHD risk, specifically in women and person with disabilities (123). The lack of sufficient data regarding appropriate exercise prescription guidelines and exercise responses in persons with MS across the range of disabilities is a major obstacle to convincing health care professionals to incorporate exercise prescription into their existing treatment of patients with MS.

Current national physical activity guidelines, which recommend frequent, nonvigorous forms of physical activity accumulating 30 minutes of activity each day, may be attainable by persons with mild to moderate MS. Although Petajan et al. (86) and Shapiro et al. (108) examined the effect of exercise on circulating levels of TG and HDL-C, neither study evaluated changes in plasma insulin in response to exercise training, which may be particularly important in persons who chronically use corticosteroids. Thus, future research should focus on the effect that physical activity may have on insulin resistance and its associated CHD risk factors.