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Cardiorespiratory Fitness and Cardiovascular Disease Risk Factors in Postmenopausal Women

Bryan L. Haddock

LOMA LINDA UNIVERSITY
School of Public Health

CARDIORESPIRATORY FITNESS AND CARDIOVASCULAR DISEASE RISK FACTORS IN POSTMENOPAUSAL WOMEN

by

Bryan L. Haddock

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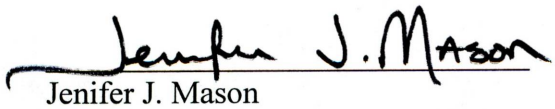
Each person whose signature appears below certifies that this dissertation, in his/her opinion, is adequate in scope and quality as a dissertation for the degree Doctor of Public Health.

Helen P. Hopp, Chairman
Associate Professor of Health Promotion and Education

Glen G. Blix
Associate Professor of Health Promotion and Education



Jenifer J. Mason
Assistant Professor of Health Promotion and Education

ABSTRACT OF THE DISSERTATION

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Helen P. Hopp, Chairman

In spite of the reductions in cardiovascular disease mortality over the last several years, cardiovascular disease remains the number one cause of death in the U.S. Prior to menopause, women have approximately 2.5-4.5 times lower risk of cardiovascular disease than do men of a similar age. Within about 10 years following menopause, however, the rate in women becomes similar to that seen in men. Increased cardiorespiratory fitness and use of hormone replacement have been suggested as ways to improve the cardiovascular disease (CVD) risk profile. Unfortunately, very little is known about the effect of cardiorespiratory fitness on the CVD risk profile in postmenopausal women, and if there is an effect whether this effect is independent of hormone status. Therefore, the purpose of this study was to determine if cardiorespiratory fitness is associated with an improvement in the CVD risks of total

cholesterol, HDL cholesterol, TC/HDL ratio, triglycerides, and fibrinogen, in postmenopausal women. Records of non smoking postmenopausal women who completed a preventive medicine physical examination, in the Aerobic Center Longitudinal Study between 1987 and 1995, were examined. Cardiorespiratory fitness was determined by total treadmill time to exhaustion on a graded exercise test, CVD risk factors were assessed via blood analysis. On cross sectional analysis, fitness was statistically significantly associated with a decrease in total cholesterol (R^2 =.08), the total cholesterol/HDL cholesterol ratio (R^2 = .12), triglycerides (R^2 = .09), and fibrinogen (R^2 = .06), and an increase in HDL cholesterol (R^2 = .04). All relationships were significant at a p value of <0.005. After statistically controlling for hormone status, age, year of testing, and blood glucose, each CVD risk factor remained significantly associated with cardiorespiratory fitness ($p<0.05$). This study indicates that cardiorespiratory fitness is an important independent determinant of blood lipid and fibrinogen levels in nonsmoking postmenopausal women.

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CHAPTER 1: INTRODUCTION

Statement of the Problem

Mortality from cardiovascular disease (CVD) has declined in recent years. In 1980 diseases of the heart constituted 38.3% of all deaths in the United States. As of 1993 diseases of the heart made up 32.6% of all deaths. Nevertheless, CVD remains the number one cause of death, with cancer being the second leading cause of death accounting for 23.4% of deaths (U.S. Department of Commerce, 1995).

Decreasing the prevalence of CVD is a major emphasis of Healthy People 2000, (DHHS, 1991). As of 1987 it was estimated that for every 100,000 people in the population, 135 would die of coronary heart disease (a major component of CVD). The listed goal is that by the year 2000 no more than 100 people will die of coronary heart disease for every 100,000 in the population.

Mortality from CVD is not the only concern, but the quality of the later years of life are important. The average life expectancy in the U.S. has risen to over 73 years. Unfortunately, almost 12 of these years are spent in an unhealthy state (DHHS, 1991). Reducing the prevalence of CVD will not only reduce mortality, expanding the average life expectancy, but will increase the number of years people are living a healthy and enjoyable life.

In the past, discussions of the high rates of CVD have typically focussed on men. This is likely due to the fact that prior to menopause women are at a decreased risk for heart disease, with men having somewhere between 2.5-4.5 times the risk of women at similar ages (Kalin & Zumoff, 1990). Within about 10 years following menopause,

however, the risk of cardiovascular disease increases to a level similar to that seen in men (Kafonek, 1994).

Increases in physical activity, resulting in improved cardiorespiratory fitness, has been shown as a way to decrease the prevalence of CVD (Paffenbarger et al., 1986; Powell, et al., 1987; and Blair et al., 1996). In 1990 the American College of Sports Medicine (ACSM) published guidelines for the amount of exercise necessary to develop and maintain cardiorespiratory fitness (Table 1.1) (ACSM, 1990). Unfortunately, most Americans do not get in as much physical activity as they need. In 1996 the Surgeon General's report on physical activity and health suggested that Americans accumulate 30 minutes of moderate activity on most if not all days of the week. It is expected that this amount of activity will significantly reduce the risk of heart disease (Surgeon General's report, 1996). As of 1985 only 22% of people in the U.S. over the age of 18 participated in 30 minutes or more of moderate activity at least five days per week. If seven days a week were used as the criteria, only 12% of the population was active at this level (DHHS, 1991).

Table 1.1 ACSM Guidelines on the Amount of Exercise Necessary for Improvements in Cardiorespiratory Fitness:

Program	**Recommendation**
Frequency of training	3-5 days per week
Intensity of training	60-90% of maximum heart rate, or 50-85% of maximum oxygen uptake or heart rate reserve.
Duration of training	20-60 minutes of continuous aerobic activity

ACSM (1995)

The increased risk of CVD seen in women following menopause is at least partially mediated through changes in blood lipid and fibrinogen levels (Jensen, Nilas, & Christinasen, 1990; Matthews et al., 1989; Razay, Heaton, & Bolton, 1992; Stevenson, Crook, & Godsland, 1993; and Folsom, 1995). In addition, the reduced incidence of CVD found with increases in physical activity and cardiorespiratory fitness is also at least partially mediated through changes in blood lipid (Durstine & Haskell, 1994) and fibrinogen levels (Ernst & Resch, 1993). However, the majority of research on the effect of exercise and cardiorespiratory fitness has been done on men. In spite of the fact that the risk of CVD significantly increases in women following menopause, most of the studies on changes in CVD risk factors with increased physical activity and cardiorespiratory fitness have not addressed this group.

Studies of postmenopausal women are further complicated by the use of hormone replacement, specifically estrogen and progestin. Hormone replacement can have a significant impact on many cardiovascular disease risk factors including blood lipids and fibrinogen (Lobo, 1991; Lee, Lowe, Smith, & Tunstall-Pedoe, 1992). Therefore, when examining the effect of physical activity and fitness on cardiovascular disease risk factors in postmenopausal women, hormone replacement status should be considered.

Purpose of the Study

Higher levels of physical activity and cardiorespiratory fitness will help reduce the risk of cardiovascular disease (CVD) in both men and women (Paffenbarger, et al., 1986; Powell, et al., 1987; Blair et al., 1989; Blair, Kohl, & Barlow, 1993; Blair et al., 1996). To date only two studies have examined the effect of exercise on blood lipid levels in

postmenopausal women, while controlling for the use of hormones (Lindheim et al., 1994; Binder, Birge, & Kohrt, 1996). No study has examined the relationship between exercise or fitness, hormone status, and fibrinogen level. In addition, an objective measure of cardiorespiratory fitness has never been used in a study of postmenopausal women and any CVD risk factors, while controlling for hormone status.

The purpose of this study was to determine if postmenopausal women with higher levels of cardiorespiratory fitness have an improved cardiac risk profile as indicated by plasma levels of total cholesterol, HDL cholesterol, total cholesterol/HDL ratio, triglycerides, and fibrinogen. Further, this study determined whether cardiorespiratory fitness was independently related to each of these risk factors, above the effects of hormone replacement and other possible confounding factors. Hormone replacement therapy as defined by the use of unopposed estrogen, and a combination of estrogen and progestin, was statistically controlled, while examining the relationship between cardiorespiratory fitness and CVD risk factors.

Importance to Preventive Care

Cardiovascular disease (CVD) is the leading cause of death in the United States (United States Department of Commerce, 1995). Increased physical activity leading to increased cardiorespiratory fitness is often recommended by Preventive Care Specialists and other health care providers as a way to reduce an individual's risk of CVD. Recommendations from the Centers for Disease Control and Prevention and the American College of Sports Medicine have stressed the importance of increased physical activity as a way to reduce the risk of CVD (Pate et al., 1995).

In spite of the evidence of reduced CVD with increased exercise and improved fitness, the majority of Americans are inactive, and this level of inactivity is the greatest in women of postmenopausal age (Piani & Schoenborn, 1993). Therefore, at the age in which women are increasing their risk of cardiovascular disease and need to find ways to decrease their risk, they are increasing their risk through a more sedentary lifestyle.

Part of the problem could be that postmenopausal women may not see the need to exercise. If CVD is a concern, some women would rather rely on the reduced risk due hormone replacement instead of increasing exercise. The current published literature lacks data showing that postmenopausal women who take hormones can further reduce their risk of cardiovascular disease with a fitness program. In addition, there are women who do not want to take hormone replacement because of a fear of increased cancer risk. If improved fitness is found to be related to a reduced CVD risk, then this would provide another option instead of just hormone replacement to reduce the risk in this population. This study of the association between cardiorespiratory fitness, and CVD risk factors helps us understand how postmenopausal women may differ from other populations. Future research can be based on this research and help us understand how to best tailor a fitness program for postmenopausal women.

Research Questions

It is expected that the beneficial effects of exercise and improved cardiorespiratory fitness occur independent of hormonal status. In a review of the literature on the benefits of exercise and fitness on cardiovascular disease risk factors (Durstine & Haskell, 1994), no mention is made about possible differences among postmenopausal women and other

populations such as premenopausal women, or males. It is unclear if a relationship exists between cardiorespiratory fitness and CVD risks, beyond the benefit of hormone replacement. Therefore, the following research questions were posed:

1. Is cardiorespiratory fitness, as measured by total time to exhaustion on a treadmill test, related to total cholesterol, HDL cholesterol, total cholesterol/HDL cholesterol ratio, triglycerides, and fibrinogen in postmenopausal women?
2. Do these CVD risk factors vary significantly in postmenopausal women who take unopposed estrogen, estrogen and progestin, and those who do not take hormone replacement?
3. If there are relationships between cardiorespiratory fitness or homone replacement and these CVD risk factors, are those relationships independent of other confounding factors?

Theoretical Basis for the Study

The risk of cardiovascular disease increases following menopause to a level similar to that seen in men (Kafonek, 1994). The mechanism of this increased risk is multifactoral, but is likely related to changes in blood lipids (Stevenson, Crook & Godsland, 1993) and blood fibrinogen (Folsom, 1995).

Following menopause many women take hormone replacement either in the form of unopposed estrogen, or a combination of estrogen and progestin. Research on the effects of these hormones on blood lipids and fibrinogen levels has yielded somewhat mixed results. In general, however, unopposed estrogen is postulated to decrease total cholesterol and fibrinogen, while increasing HDL cholesterol and triglycerides. The

addition of progestin is thought to decrease both HDL cholesterol and triglycerides from levels found with unopposed estrogen toward that seen in women who do not take hormone replacement (Lobo, 1991; Lee et al., 1992; Nabulsi et al., 1993). The typical changes seen following menopause and then with hormone replacement are shown in Table 1.2.

Table 1.2 Changes in Blood Lipid and Fibrinogen Level with Menopause and Hormone Replacement

	Following menopause without hormone replacement	**Use of unopposed estrogen**	**Added progestin to estrogen**
Total cholesterol	↑	↓	NC
HDL cholesterol	↓	↑	↓
Triglycerides	↑	↑	↓
Fibrinogen	↓	↓	NC

Note: Changes in unopposed estrogen are compared to taking no hormone replacement. Changes with added progestin are compared to unopposed estrogen.

Studies on the effect of exercise, or increased fitness, on blood lipids and fibrinogen, in postmenopausal women, are limited. The vast majority of studies have not distinguished between postmenopausal women and the rest of the population in spite of the many changes that occur in these risk factors with menopause. Further hormone replacement is seldom considered in exercise and fitness studies. It is expected, however, that increased exercise and fitness will lead to an increase in HDL cholesterol, and a decrease in triglycerides and fibrinogen (Durstine & Haskell, 1994; Ernst, 1993).

Based on the impact that both a fitness program and hormone replacement are expected to have on CVD risk factors, it seems reasonable to examine effects of a fitness program on postmenopausal women while controlling for hormone replacement. To date only two published studies have done this (Table 1.3) (Lindheim et al., 1994; Binder, Birge, & Kohrt, 1996). The first of these (Lindheim et al., 1994) examining the relationship between exercise, unopposed estrogen, and blood lipid levels. The second study (Binder et al., 1996) examined this same relationship, except that Progestin was added to the estrogen and the amount of exercise differed significantly from the first study.

Table 1.3 Studies on the Combined Effect of Exercise and Hormone Replacement

	Lindheim et al., 1994	**Binder, Birge, & Kohrt, 1996**
Length of follow up	6 months	11 months (9 months of aerobic exercise)
Sample size	101 postmenopausal women divided into four groups: Control, Exercise, Hormone replacement, Both exercise and progestin	71 postmenopausal women divided into four groups: Control, Exercise, Hormone replacement, Both exercise and hormone replacement
Exercise intensity	70% of maximum heart rate	70-85% of maximum heart rate
Duration of exercise session	15 minutes	45 minutes
Frequency of exercise	3 days per week	3 or more days per week
Type of hormone replacement	Daily estrogen	Daily estrogen with progestin for 13 days every third month
Outcome measures	Blood lipids	Blood lipids

My study went beyond previous studies to fill the following gaps:

1. An objective measure of fitness was used, allowing an analysis that takes into consideration a wide range of fitness levels. Also, an objective measurement of fitness limited problems inherent in self reported exercise, and differing levels of effort during an exercise program.
2. Differences between those not taking hormone replacement, those taking estrogen only, and those taking a combination of estrogen and progestin was examined.
3. Blood fibrinogen was assessed in addition to blood lipid levels.

CHAPTER 2: REVIEW OF THE LITERATURE

Introduction

Menopause occurs in essentially all women by the age of 58, although the age at which women reach this point can vary tremendously (Kannel & Gordon, 1987). Prior to menopause women are at a decreased risk for heart disease, with men having 2.5-4.5 times the risk of women at similar ages (Kalin & Zumoff, 1990). Following menopause, women typically show increases in several cardiovascular disease (CVD) risk factors including blood lipid levels and blood clotting characteristics. Plasma levels of total cholesterol and triglycerides increase following menopause and are predictive of mortality due to CVD. The increase in total cholesterol is primarily from low density lipoprotein (LDL) which is the main atherogenic component of cholesterol. In addition, high density lipoprotein (HDL) cholesterol, which is protective of CVD, decreases following menopause. This decrease is mostly due to decreases in HDL_2 , which is more protective of CVD than its counterpart, HDL_3 (Jensen, Nilas, & Christiansen, 1990; Matthews et al. 1989; Razay, Heaton & Bolton, 1992; Stevenson, Crook, & Godsland, 1993). Finally, plasma fibrinogen also increases following menopause, increasing the risk of clot formation (Folsom, 1995). These changes in blood lipids and fibrinogen lead to the increased risk of CVD in women following menopause.

Many women take hormone replacement therapy to reduce the side effects that often accompany menopause, to prevent osteoporosis, and to help counteract some of the lipid and fibrinogen changes described above. Exercise is also recommended as a way to

improve blood lipid levels, especially HDL cholesterol and triglycerides, and decrease the concentration of blood fibrinogen.

This review presents an overview of the effects of menopause, hormonal status, aerobic exercise, and fitness on key CVD risk factors including plasma levels of total cholesterol, HDL cholesterol, total cholesterol/HDL ratio, triglycerides, and fibrinogen. In addition, the interaction of menopause, hormonal status, and exercise on these same coronary heart disease risk factors will be discussed.

Menopause and Cardiovascular Disease Risk Factors

Within about 10 years following menopause the risk of CVD increases in women to a level similar to that seen in men (Kafonek, 1994). This increase risk is thought to occur, at least partially, due to changes in blood lipid and fibrinogen levels. A summary of the typical changes seen following menopause are shown in Table 2.1.

Table 2.1 Lipid and Fibrinogen Changes Associated with Menopause

Risk Factor	Typical Changes Seen Following Menopause
Total Cholesterol	+14%
HDL cholesterol	-7%
Triglycerides	+12%
Fibrinogen	+5%

The percent given is the expected change seen following menopause above that which would be expected due to age.

Menopause and Blood Lipids

Following menopause, plasma levels of total cholesterol and triglycerides increase, while HDL cholesterol decreases. In a cross sectional analysis of 542 women, aged 18-

70, 147 (27%) of which were postmenopausal, menopause was associated with a 14% higher total cholesterol level and a 27% higher LDL cholesterol. In addition the total HDL cholesterol was 7% lower in the postmenopausal women. This lower level of HDL occurred in spite of a 7% higher HDL_3 level. The HDL_2, which is thought to be the more protective of CVD than HDL_3, was 25% lower in postmenopausal women. Plasma levels of triglyceride increased with age in this group of women; however, the change from premenopausal to postmenopausal status was associated with an additional 12% higher triglyceride level than could be explained by age alone (Stevenson, Crook, & Godsland, 1993).

In a longitudinal study of 541 initially premenopausal women, aged 42-50, all increased their total cholesterol, LDL cholesterol, and triglycerides. During the 2.5 years of follow-up 69 women (13%) went through natural menopause, and these women demonstrated a greater increase in these plasma lipid levels than those who remained premenopausal. Therefore, some of the lipid changes are apparently due to aging, but menopause seems to have its own independent effect above the effects of age. The HDL level decreased significantly in those women who went through menopause, whereas those who stayed premenopausal showed no change in HDL cholesterol (Matthews et al., 1989). Another longitudinal study also found the change from premenopausal to postmenopausal status was associated with significantly increased levels of total cholesterol, LDL cholesterol, and triglycerides, while HDL levels decreased significantly (Jensen, Nilas, & Christiansen, 1990).

Although some question exists as to the independent effect of menopause above the effects of age, there is general agreement that postmenopausal women typically have higher levels of total cholesterol, LDL cholesterol, and triglycerides than premenopausal women of the same age. Postmenopausal women also tend to have decreased levels of HDL cholesterol. These changes in blood lipids could account for at least some of the increased risk of heart disease seen following menopause.

Menopause and Fibrinogen

In the Atherosclerosis Risk in Communities Study (ARIC), postmenopausal women had fibrinogen levels that were 8.4 mg/dL higher than premenopausal women of a similar age (Folsom et al., 1991). Meade, Haines, Imeson, Stirling, and Thompson (1983), in the Northwick Park Heart Study in London, examined 841 women aged 18-59 and found age adjusted plasma fibrinogen levels to be significantly higher in postmenopausal women (3.16 g/L) compared to premenopausal women (3.08 g/L). Likewise, a cross sectional study of women aged 45-54 found that postmenopausal women who were not receiving hormone replacement had fibrinogen levels that were approximately 5% higher than premenopausal women of a similar age (Scarabin, et al., 1993). Lee, Lowe, Smith, and Tunstall-Pedoe (1992) measured plasma fibrinogen level on 4837 women aged 25-64 in the Scottish Heart Study and found that postmenopausal women, whether surgically or naturally, had higher blood fibrinogen levels than premenopausal women following standardization for age.

In a review of the epidemiology of fibrinogen, Folsom (1995) concludes that plasma fibrinogen levels increase with age, with women having higher values than men, and the

level of fibrinogen increases further following menopause. The amount of increase in fibrinogen associated with menopause seems to be about 5-6%.

Cardiovascular Disease Risk Factors

Total Cholesterol

Since the 1960s the average total cholesterol has dropped for most Americans. Presently the average American female has a total cholesterol of 207 mg/dL with the values typically increasing with age up to 237 mg/dL in females between the age of 55-64 (Johnson, et al., 1993). A total cholesterol of greater than 200 significantly increases an individual's risk of CVD (ACSM, 1995). In addition, many Americans still have a total cholesterol of greater than 240 mg/dL, and are therefore at a significant risk for CVD (Sempos et al., 1993). The link between total cholesterol and CVD has been well established. In the Lipid Research Clinics Coronary Primary Prevention Trial (LRC-CPPT), researchers found that lowering total cholesterol led to a significant decrease in the incidence of coronary heart disease (a form of CVD). This study, however, was performed only on men (LRC-CPPT, 1984). The Framingham data included both men and women and demonstrated an increased risk of CVD with increased total cholesterol for both sexes (Anderson, Castelli, & Levy, 1987). In a review of 19 cholesterol lowering trials, of which seven trials included women, the authors concluded that a 1% reduction in total cholesterol was associated with an approximate 2.5% drop in the incidence of CHD (Holme, 1990). The current evidence suggests that total cholesterol is a strong risk factor for CVD in both men and women.

HDL Cholesterol

According to the American College of Sports Medicine (1995), an HDL cholesterol of less than 35 mg/dL is considered a significant risk factor for CVD, whereas an HDL

cholesterol above 60 is considered protective, and therefore a negative risk factor for CVD (ACSM, 1995). Since total cholesterol and HDL are both important risk factors for CVD, the combination of the two expressed as the total cholesterol/HDL cholesterol ratio, is often considered of even greater importance (Linn, et al., 1991). A ratio of less than 3.0 is considered optimal, while a ratio greater than 5.0 is considered to be high risk (Stampfer, Sacks, Salvini, Willett, & Hennekens, 1991). The average American female has a total cholesterol/HDL ratio of 4.0 (Linn, et al., 1991).

A negative association between total HDL and CVD has been demonstrated in the Framingham Heart Study data which indicate that HDL cholesterol has a significant negative association with CVD incidence in both men and women. Their research demonstrated that those with HDL cholesterol values less than 35 mg/dL had more than eight times the risk of developing coronary heart disease as those with HDL cholesterol values greater than 65 mg/dL (Gordon, Castelli, Hjortland, Kannel, & Dawber, 1977).

Gordon et al. (1989), in a review of four major studies including the Framingham Heart Study, the Lipid Research Clinics Prevalence Mortality Follow up Study, the Coronary Primary Prevention Trial, and the Multiple Risk Factor Intervention Trial, found that HDL was associated with a lower risk of CVD independent of age, blood pressure, smoking, body mass index, and LDL cholesterol. In the Framingham Heart Study, Coronary Primary Prevention Trial, and Multiple Risk Factor Intervention Trial studies, a 1% increase in HDL led to a 2% decrease in coronary heart disease in men, and in the Framingham Heart Study the same 1% increase in HDL led to a 3% decrease in CVD for women. In the Lipid Research Clinics Prevalence Mortality Follow-up Study,

where only fatal outcomes were recorded, a 1% increase in HDL led to a reduced risk of mortality from coronary heart disease of 3.7% in men and 4.7% in women. It appears that HDL cholesterol may be an even more important risk factor for CVD in women than in men.

Triglycerides

Ideal triglyceride levels are seen as less than 110 mg/dL (Haskell, 1984). Follow up studies have typically reported an association between plasma triglyceride levels and CVD. Miller et al. (1992) followed a group of 740 women for 15 years, after they had received an angiogram. A high triglyceride level (>150 mg/dL) was significantly associated with future CVD mortality (RR=2.0). In the Framingham study, Castelli (1992) found that the incidence of CVD was higher in women, with a higher level of triglycerides, however this relationship did not hold for men. This association between triglycerides and CVD in women held following adjustment for HDL cholesterol. In the Lipid Research Clinics Follow-up study, an increased triglyceride level was associated with fatal cardiovascular events on univariate analysis. However, following statistical adjustment for HDL and LDL cholesterol levels, smoking status, systolic blood pressure, body-mass index, blood glucose, and hormone replacement, triglycerides were not significantly associated with cardiovascular disease mortality in men or women. (Criqui et al., 1993). Looking at the same data, however, Bass, Newschaffers, Klag, & Bush (1993) reported that a triglyceride level of >200 mg/dL was independently associated with CVD risk in women. The difference in analyses of the same data is likely due to the

fact that the second study examined only those persons with high triglycerides, instead of all values.

In a prospective study, 1462 women aged 38-60 at baseline, were followed over a 20 year period. Serum triglycerides were reported as an independent risk factor for CVD, with a relative risk of 1.86 (95% C.I. = 1.30-2.67) for those in the highest quartile compared to the lower three quartiles. (Bengtsson, Bjorkelund, Lapidus, & Lissner, 1993).

A review of cross sectional studies indicates that the majority show a significant relationship between triglycerides and CVD, and this association is stronger in women than in men, especially when comparing older men and women (Austin & Hokanson, 1994). The relationship between triglycerides and CVD continues to be debated. However, it appears that triglycerides are an important risk factor for CVD in women.

Fibrinogen

The average level of fibrinogen in women is around 300 mg/dL, with increasing levels associated with an increased risk of CVD (Folsom, et al., 1991). In the Framingham study, Kannel, Wolf, Castelli, and D' Agostino (1987) measured the plasma fibrinogen level in 1315 subjects (554 men and 761 women), ranging in age from 47-79, all of whom were free of CVD at the time of measurement. After 12 years of follow up, the investigators found the risk for CVD increased with increasing levels of fibrinogen in both men and women. In support of this proposed association between fibrinogen and CVD, a large analysis of 3,000 patients suffering from angina and undergoing

angiographic evaluation found fibrinogen level significantly associated with vascular occlusion in both men and women (ECAT Angina Pectoris Study Group, 1993).

Authors of a meta analysis of six prospective studies concluded that serum levels of fibrinogen were significantly associated with CVD. The odds ratio of future myocardial infarction, stroke, or peripheral arterial disease across the studies was 2.3 for those with fibrinogen levels in the highest tertile compared to the lowest tertile (Ernst & Resch, 1993). Meade (1995), in a review of the literature on the effects of plasma fibrinogen level on heart disease, concluded that elevated fibrinogen levels are significantly associated with the incidence of ischemic heart disease, with the association being about as strong as that found with elevated cholesterol and ischemic heart disease.

Those with high fibrinogen have a further increase in risk because of an association with a number of other CVD risk factors including smoking, obesity, diabetes, hypertension, LDL cholesterol, triglycerides, and social economic status (Folsom, 1995). Therefore, those with high levels of serum fibrinogen are at a significantly increased risk of CVD.

Hormone Replacement Therapy and the Prevention of Cardiovascular Disease

Postmenopausal women taking unopposed estrogen replacement therapy show a reduction in CVD of approximately 50% compared to those not taking hormone replacement therapy (HRT), although the amount of this decrease varies depending on the particular study cited (Bush et al., 1987; Barrett-Conner & Bush, 1991).

Progestin is frequently added to estrogen supplementation in women who have gone through natural menopause, in order to reduce the risk of endometrial cancer, and

possibly breast cancer (Whitehead, Hillard, & Crook, 1990). The effect of this added progestin on CVD outcomes however has not been studied.

Lipid Research Clinics Program Follow-up Study

A cohort of 2270 women, aged 40-69 at baseline, all who were a part of the Lipid Research Clinics Prevalence Study of cardiovascular disease, between 1972 and 1976, were followed prospectively for an average of 8.5 years. Estrogen status was determined at baseline by the use of estrogens within the two weeks prior to their clinic visit. In this cohort of women, 593 (26%) were taking estrogen replacement, and 1677 (74%) reported no use of estrogen replacement. Only 6 (1%) of estrogen users were also taking progestin replacement. At baseline, there were no significant differences between those using estrogen and those not using estrogen, as to the prevalence of CVD or risk factors for CVD. Following the first 5.5 years of the study, those taking estrogen replacement alone had a significant lower risk (R.R. = 0.37) for all cause mortality compared to those not taking estrogen. After 8.5 years, the relative risk for those taking estrogen replacement continued to be significantly lower with a relative risk of 0.54 for all cause mortality. When examining CVD mortality, estrogen users had a significantly reduced relative risk of 0.34 compared to women not using estrogen, following adjustment for age. Those women taking estrogen also had significantly higher HDL cholesterol and triglyceride levels, and significantly lower LDL cholesterol levels. When adjustment was made for the risk factors of age, smoking, and blood pressure, the significant negative association between CVD mortality and estrogen use remained. The authors estimate that

approximately 50% of the beneficial effects of estrogen can be attributed to changes in LDL and HDL cholesterol (Bush, et al., 1987).

Nurses Health Study

The Nurses Health Study, initiated in 1976, examined a total of 121,700 nurses as part of an ongoing study of heart disease in women. Participants were asked a variety of questions including information on their menopausal and hormonal status. A cohort of 48,470 postmenopausal women were followed during a 10 year follow up. The age adjusted relative risk of a major coronary event for current users of estrogen was 0.51 (95% C.I. = 0.37-0.70) compared to those who had never used estrogen replacement. Those women who formerly used estrogen did not have a significantly reduced risk of a major coronary event, compared to those who had never used estrogen (R.R. = 0.91, 95% C.I. = 0.73-1.14) (Stampfer et al., 1991). This compares with the data from four years of follow up in which both current and former use of estrogen was associated with a reduced risk of major coronary events (Stampfer et al., 1985).

Framingham Study

Unlike the majority of studies on estrogen replacement therapy, the Framingham study found that estrogen replacement therapy was associated with an increased risk of CVD, showing a significantly increased relative risk of 1.76 for those taking estrogen compared to those not taking estrogen in a cohort of 1,234 postmenopausal women (Wilson, Garrison, & Castelli, 1985). The differences in this study are probably due to methodological differences between Framingham and other studies on hormone replacement therapy. Age could be a factor since the women in the Framingham study

were older. In the Framingham study, older women were less likely to use hormone replacement. The main reason, however, was likely that the Framingham data was adjusted for HDL cholesterol level, which is considered to be one of the cardiovascular benefits of estrogen replacement therapy. In addition, angina pectoris was used as an end point, which may be an unreliable indicator of CVD, rather than death or some other objective measure (Kafonek, 1994).

Therefore, the majority of evidence supports the relationship between a reduced risk of cardiovascular disease with the use of estrogen replacement. It is unknown if this same effect would be evident if progestin is taken along with the estrogen.

Hormone Replacement Therapy and Cardiovascular Disease Risk Factors

The risk of cardiovascular disease decreases among women on hormone replacement, particularly estrogen. Much of this decreased risk has been attributed to the effect of hormone replacement on blood lipid levels. However, other factors such as fibrinogen may also play a significant role in reducing the risk of cardiovascular disease (Bush et al., 1987; Henderson, Paganini, & Ross, 1988; Stampfer & Colditz, 1991).

Hormone Replacement Therapy and Total Cholesterol

In the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (1995), total cholesterol was significantly decreased in postmenopausal women only when estrogen and progestin were taken together. Those taking unopposed estrogen showed a decrease in LDL cholesterol similar to the decrease seen in those taking both estrogen and progestin, but their HDL increased as well, resulting in less of a change in total cholesterol, but improving the total cholesterol/HDL ratio. Long term studies of hormone

replacement have typically shown a reduction in total cholesterol among women on both unopposed estrogen or a combination of estrogen and progestin (Gambrell & Teran, 1991). In the Atherosclerosis Risk in Communities study, Nabulsi et al. (1993) studied 4958 women who were assigned to one of four groups: current users of unopposed estrogen, current users of estrogen with progestin, non users of hormones who formerly used them, and non users of hormones who had never used them. The results demonstrated that those who currently used unopposed estrogen or a combination of estrogen and progestin had a significantly lower levels of total and LDL cholesterol than those who had never taken hormone replacement therapy. Though most studies point to an association between the use of hormone replacement and lower cholesterol, a study of 50 postmenopausal women did not show a decrease in total cholesterol after one year of estrogen and progestin (Omu & Al-Qattan, 1996).

In summary the weight of the evidence suggests that total cholesterol is significantly lower in postmenopausal women who take estrogen replacement, with the addition of progestin having no significant impact on the total cholesterol level. According to a review by Lobo (1991), estrogen replacement therapy lowers the total cholesterol by about 6% in postmenopausal women.

Hormone Replacement Therapy and HDL Cholesterol

Unopposed estrogen replacement is thought to increase the plasma level of HDL cholesterol. One study showed that one year on conjugated equine estrogens (0.625 mg/day) increased HDL levels by 13.5% (Barnes, Roy, & Lobo, 1985). Several authors postulate that adding progestin to estrogen replacement therapy may negate some of the

beneficial effects of estrogen therapy on HDL cholesterol levels (Hirvonen, Malkonen, & Manninen, 1981; Crona, 1986; Omu & Al-Qattan, 1996).

The mechanism by which progestin is thought to decrease HDL is through an increase in hepatic lipase activity and the degradation of HDL cholesterol. Lobo, (1991) has speculated that if progestin is used only 10-12 days per month, the endometrium will still be protected, and that this level of progestin may not negate the beneficial effects of estrogen on HDL cholesterol (Lobo, 1991). This hypothesis seems to be confirmed by the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI) in which unopposed estrogen increased HDL cholesterol by 5.6 mg/dL over those not taking hormone replacement. Those women who took a combination of estrogen and progestin also increased HDL by 4.1 mg/dL if progestin was taken for only 12 days per month. If progestin was added to the estrogen replacement each day the increase was only 1.2-1.6 mg/dL greater than those not taking any hormone replacement. Therefore, according to the results of the PEPI trial, even though progestin may reduce the beneficial effects of unopposed estrogen replacement on HDL, the majority of the increase in HDL cholesterol can be maintained if progestin is only used for 12 days per month (PEPI Trial Group, 1995).

Other researchers have failed to find decreases in HDL with the addition of progestin. Gambrell & Teran, (1991) in a group of postmenopausal women (<1 yr. to 30 yrs. postmenopausal) HDL cholesterol was not significantly different in those on unopposed estrogen as compared with those who added progestin. Therefore, the authors claim that there are no negative effects on HDL cholesterol, with long term addition of progestin.

In the Atherosclerosis Risk in Communities Study of 4958 postmenopausal women, those who currently used hormone replacement therapy, whether unopposed estrogen or a combination of estrogen and progestin, had a significantly higher HDL cholesterol than those not using hormones. There were no significant differences in those taking estrogen alone and those using estrogen and progestin (Nabulsi et al., 1993).

It is clear that unopposed estrogen replacement therapy increases HDL cholesterol in postmenopausal women. The effects of adding progestin to estrogen on HDL cholesterol levels are, at this point, uncertain and in need of further research.

Hormone Replacement Therapy and Triglycerides

Unlike the positive effects estrogen has on total and HDL cholesterol, estrogen replacement therapy tends to raise triglyceride levels (Lobo, 1991) The amount of increase in triglycerides seems to be dependent on the type and amount of estrogen used (Samsioe, 1994). In the Postmenopausal Estrogen/Progestin Interventions Trial (PEPI, 1995), women taking estrogen replacement therapy increased their level of plasma triglycerides by 13% over a three year period compared to a group taking a placebo. This increase was similar for those taking unopposed estrogen or a combination of estrogen and progestin.

Crook et al., (1992) found oral unopposed estrogen to raise triglyceride levels while the addition of progestin reduced plasma triglyceride levels. In the Atherosclerosis Risk in Communities study, Nabulsi et al. (1993) performed a cross sectional analysis of 4958 postmenopausal women and found those taking unopposed estrogen had significantly higher triglyceride levels than those not taking hormone replacement therapy. The

addition of progestin lowered the triglycerides by 10 mg/dL to a level that was not significantly different from those not taking hormone replacement. In contrast Jensen, Riis, Strom, Nilas, & Christianson, (1987) examined 45 postmenopausal women who were assigned to a hormone replacement or placebo group. Those in the hormone replacement group received unopposed estrogen for 12 months, followed by 12 months with estrogen and 12 days per month of progestin. No significant differences were observed in triglycerides with the use of unopposed estrogen compared to the placebo group. The addition of progestin in the second 12 month cycle also did not alter triglycerides.

Based on the current evidence, it appears that unopposed estrogen replacement tends to increase plasma triglycerides, while the addition of progestin to estrogen replacement may reduce triglycerides to the level seen in those not taking hormone replacement therapy.

Hormone Replacement Therapy and Fibrinogen

Lee, Lowe, Smith, & Turnstall-Pedoe (1992), in a cross sectional analysis of postmenopausal women, found that those currently taking hormone replacement therapy, either unopposed estrogen or a combination of estrogen and progestin, had lower fibrinogen levels than those not taking any hormone replacement, following adjustment for age and smoking status. Similarly, the Atherosclerosis Risk in Communities cross sectional analysis of 4958 postmenopausal women found that those taking unopposed estrogen or a combination of estrogen and progestin had a significantly lower fibrinogen level than those not taking hormone replacement therapy. There was no difference in

fibrinogen levels between those taking unopposed estrogen or a combination of estrogen and progestin (Nabulsi et al., 1993). These results indicate that progestin does not significantly affect plasma fibrinogen. In support of these findings, Scarabin et al. (1993) tested a group of 293 healthy women aged 45-54 and found that those who were postmenopausal had higher fibrinogen levels, but those postmenopausal women who were taking hormone replacement therapy (a combination of estrogen and progestin) had fibrinogen levels similar to the premenopausal women.

It appears that hormone replacement therapy in postmenopausal women decreases fibrinogen level. In addition the decreased fibrinogen with hormone replacement is found whether using unopposed estrogen or a combination of estrogen and progestin.

Exercise and Cardiovascular Disease

Evidence has continued to accumulate documenting the effect of aerobic exercise, and subsequent increases in fitness, on decreased risk of heart disease. Paffenbarger et al. (1986), in a longitudinal study of Harvard alumni, found that individuals who expended greater than 2000 Kcal per week had an overall 28% lower risk of death than those who expended less than 2000 Kcal per week. Most of this reduced risk was reported to be from a reduction in CVD deaths. In addition there was a consistent trend toward a lower death rate as physical activity increased from those who engaged in the least activity to those with the most activity. In a review of studies on physical activity and heart disease Powell et al. (1987) concluded that a person with a sedentary lifestyle is twice as likely to develop heart disease as are the most active individuals. In addition, in a prospective study of 40,417 postmenopausal women found that those who participated in moderate

activity one time or more per week had a relative risk for mortality of 0.78 (95% CI, 0.64-0.96) (Kushi, Fee, Folsom, Mink, Anderson, & Sellers, 1997).

A possible bias exists in the results on physical activity and death, since the reports of exercise are based on self reports. There was a need for more objective data regarding the effect of physical activity on CVD risk factors. Results from the Cooper Institute for Aerobics Research (CIAR) have shown that men and women who achieve a moderate level of fitness can significantly reduce their risk of both all cause and CVD mortality. In the CIAR study, 25,341 men and 7080 women, participants were divided into quintiles of fitness. Males and females in the least fit quintile were over twice as likely to die of CVD than were those in the most fit quintile (Blair et al. 1989; Blair et al. 1996). Interestingly, this same reduced risk of mortality with higher levels of cardiorespiratory fitness was not found with self reported physical activity in women. The authors point out the possible inadequate assessment of physical activity from the self reports (Blair, Kohl, & Barlow, 1993). Measured cardiorespiratory fitness takes into account all activity, even non structured exercise. In order to show that this association with fitness and mortality, in the CIAR data, was not due to self selection bias, Blair et al. (1995) found that those who were unfit at an initial testing, but improved their fitness in future years, also benefited with reduced mortality.

Because of these and other research projects, in 1991 the American Heart Association, added physical inactivity as one of the four leading risk factors for CVD. Current recommendations for the Centers for Disease Control and Prevention and the American College of Sports Medicine are that adults in the U.S. should accumulate 30

minutes or more of moderate intensity physical activity on most, and preferably all, days of the week. Moderate intensity exercise was defined as exercising at an intensity that would elevate the metabolism three to six times the resting rate. Moderate intensity exercise could be defined as walking at three to four miles per hour for most healthy adults (Pate et al., 1995).

Exercise and Total Cholesterol

In a review by Durstine & Haskell (1994), exercise and improved fitness were associated with reduced total cholesterol levels, but this association was no longer significant after adjusting for age, body weight, and diet. Much of the research on the effect of exercise has been done on men or a combination of men and women. In research on females, the results vary with some studies showing exercise to be related to a lower total cholesterol (Busby, Notelovitz, Putney, & Grow, 1985; Lindheim, 1994; Shephard, Youldon, Cox, & West, 1980; and Brownell, Bachorik, & Ayerle, 1982) and other studies showing no association (Cauley et al., 1986, Durstine et al., 1987; Hardman, Hudson, Jones, & Norgan, 1989; Wynn, Frey, Laubach, & Glueck, 1980; Rotkis, Boyden, Stanforth, Pamenter, & Wilmore, 1984; Duncan, Gordon, & Scott, 1991; Hill, et al., 1989; Boyden, et al., 1987; Goodyear, Fronsoe, Van Houten, Dover, & Durstine, 1986). In a meta analysis of exercise and cholesterol by Lokey and Tran (1989), a small but significant association between total cholesterol and aerobic exercise was found, with self-reported participation in aerobic exercise leading to a 4.1 mg/dL decrease in total cholesterol, compared to those reporting no aerobic exercise.

When studying only postmenopausal women, Cauley et al. (1987) found no significant differences in total cholesterol between those participating in a two year walking program compared to inactive controls. Stevenson, Davy, & Seals (1995), in a cross sectional study of postmenopausal women, found that highly trained runners showed a non significant trend toward lower total cholesterol compared to a group of age matched inactive controls. Lindheim et al. (1994) found that six months of exercise training resulted in a significant 5% reduction in the total cholesterol level of postmenopausal women.

The discrepancies found among studies of women are likely due to differences in the amount and intensity of exercise, menopausal status, and the use of hormone replacement. Finally, if exercise and improved fitness also increases HDL cholesterol, as expected, then the effect on total cholesterol may be somewhat blunted.

Exercise and HDL Cholesterol

Increased physical activity tends to increase HDL cholesterol levels (Durstine & Haskell, 1994), although most of the research has been done on men. Results of research involving women show mixed results with some studies showing a positive association (Durstine et al., 1987; Hardman, Hudson, Jones, & Norgan, 1989; Lindheim et al., 1994; Warner et al., 1995; Rotkis, Boyden, Stanforth, Pamenter, & Wilmore, 1984; Goodyear, Fronsoe, Van Houten, Dover, & Durstine, 1986; and Hill, et al., 1989), while other studies show no association (Busby, Notelovitz, Putney, & Grow, 1985; Cauley et al., 1986; Lokey & Tran, 1989; Wynn, Frey, Laubach, & Glueck, 1980; Frey, Doerr, Laubach, Mann, & Glueck, 1982; Shephard, Youldon, Cox, & West, 1980; Boyden, et

al., 1987; and Brownell, Bachorik, & Ayerle, 1982). Lobo (1991), suggests that exercise is less effective in altering lipoprotein levels in women compared to men. Warner et al. (1995) found that in a group of cardiac rehabilitation subjects who exercised 3 days a week for 30-40 minutes, men and women increased their HDL cholesterol by 10% and 7%, respectively, over the first year of follow up. However, over the next five years the men did not further increase their HDL cholesterol whereas the women increased their HDL cholesterol by a total of 20%. At the end of the five year follow up the men only, had a 5% increase in HDL over baseline values. The authors of this study admit, however, that this greater improvement in HDL among women over five years may have been influenced by attrition, in that only 83 (12%) of the original 719 patients were available for follow up.

Some investigators suggest that exercise intensity needs to be greater than 80% of an individual's predicted maximum heart rate in order for improvements in HDL to take place. In a study of men and women Seals, Hagberg, Hurley, Ehsani, and Holloszy (1984), found that exercise increased the HDL level and decreased the total cholesterol/HDL ratio, but this only occurred if the exercise was performed at greater than 80% of maximal heart rate. Another study of older men and women showed only a non significant increase in HDL levels with 30-60 minutes of aerobic exercise, 3 times per week (Blumenthal et al. 1991). However, the intensity of exercise in this study was not as high as that seen in other studies which did show a significant increase in HDL cholesterol. However, Motoyama et al. (1995), in a study of hypertensive men and

women, found that treadmill walking at a low intensity (50% VO_2 max) for 30 minutes, 3-6 times a week did significantly increase HDL cholesterol levels.

It is accepted that there is a positive relationship between exercise and HDL cholesterol. There is still debate, however, on what is the optimal intensity and amount of exercise for improving HDL cholesterol levels.

Cross Sectional Studies of Women

In a cross sectional study of 744 women aged 18-65, cardiorespiratory fitness was significantly related to HDL levels, independent of age and weight (Gibbons, Blair, Cooper, & Smith, 1983). Their study examined both pre and post menopausal women, and they did not distinguish between the two groups, so this relationship might not hold true for postmenopausal women alone. However the association was still statistically significant after controlling for age, which would tend to be associated with menopausal status.

In a study of 75 postmenopausal women not taking hormone replacement therapy, participants were compared for their exercise habits and HDL levels. Those who exercised the most (>2000 Kcal of expenditure a week) had HDL levels of 74.7 mg/dL, which was significantly higher than the 60.1 mg/dL found in the group with the least activity (Cauley, Laporte, Kuller, & Black-Sandler, 1982). In a group of 255 postmenopausal women who were not on hormone replacement therapy, higher levels of sport related activity were shown to be significantly correlated to HDL, although the correlation was only moderate (r=0.20) (Cauley, Laporte, Black-Sandler, Orchard, Slemenda, & Petrini, 1986).

In summary, the cross sectional studies indicate that both self reported exercise and measured cardiorespiratory fitness are positively associated with HDL cholesterol level.

Follow Up Studies of Women

Suter and Marti (1992) randomized a group of pre and post menopausal, middle-aged women into an exercise group (jogging 2 hours per week, for 4 months), and a control group. The exercise group did not show a significant improvement in HDL cholesterol level. Despite this lack of significant improvement of HDL cholesterol with exercise, changes in endurance capacity were shown to be the strongest predictor of HDL and the total cholesterol/HDL ratio. Failure to show significance between the two groups was probably due to the relatively low intensity of exercise and the relatively short term nature of the study (4 months). Also, many of the women were taking oral contraceptives, which may decrease HDL cholesterol in premenopausal women.

Cauley, Kriska, Laporte, Sandler, and Pambianco (1987), in a randomized trial of 204 postmenopausal women not receiving hormone replacement therapy, found no significant effect of a two year walking program on HDL cholesterol after controlling for obesity, smoking status, and alcohol consumption. No mention was made of the intensity of exercise in this study, but the total quantity of exercise was relatively low, with the exercise group walking an average of 11.2 km (6.9 mi) per week. In another study of 17 postmenopausal women not receiving estrogen replacement who were placed on a walk/jog program 3 times a week for 8 months, there was no significant change in HDL cholesterol (Boyden, et al. 1987). This lack of significance would be expected with the low power with such a small number of subjects. Busby, Notelovitz, Putney, and Grow

(1985), studied a group of 50 women aged 40-65 who were randomized into four groups: a control group; a discussion group; an exercise group (3 times per week, 45 minutes per session, 12 weeks: 15 minutes of warm up stretching and strengthening, 30 minutes of walking at 70-80% of their age predicted maximum, and 15 minutes of cool down stretching and relaxation); and a combination discussion and exercise group (with the same exercise and discussion as the other groups). No significant changes were seen in HDL cholesterol in any of the groups. The lack of significance could be a result of the small number of subjects or the short period of follow up.

The work on HDL and exercise in women has shown mixed results. Many of these results are probably due to differences in the intensity and total amount of exercise. When more objective measures such as fitness are used, as in the study by Gibbons, Blair, Cooper, and Smith (1983), rather than self reported exercise, significant results are found. One possible explanation is that self reports of physical activity do not match actual activity. For example Blair, Kohl, and Barlow (1993) found a significant inverse relationship between fitness and mortality in women, but this relationship was not significant when comparing self reported physical activity to mortality. This indicates a possible discrepancy between self reported physical activity and actual activity as measured by fitness assessment. In addition, much of the research done on women has included both pre and postmenopausal women, with very little evidence suggesting an association between HDL cholesterol and exercise or fitness in postmenopausal women in particular. Therefore, the relationship between fitness and HDL cholesterol in postmenopausal women is still unknown.

Exercise and Triglycerides

Durstine and Haskell (1994), in a review of the literature, found that cross sectional studies of athletes and sedentary controls show lower triglyceride levels in the athletes. Most follow up studies have also shown that triglycerides will decrease with endurance training with the amount of decrease depending on the baseline level of triglyceride. Unfortunately, the majority of these studies have been performed on men, despite the fact that triglycerides may be a more important risk factor in women (Austin & Hokanson, 1994).

In research on women, exercise decreases plasma triglyceride level in some studies (Lindheim et al., 1994; Lokey & Tran, 1989; Gibbons, Blair, Cooper, & Smith, 1983), while having no effect in other studies (Busby, Notelovitz, Putney, & Grow, 1985; Cauley et al., 1986; Durstine et al., 1987; Wynn, Frey, Laubach, & Glueck, 1980; Frey, Doerr, Laubach, Mann, & Glueck, 1982; Goodyear, Fronsoe, Van Houten, Dover, & Durstine, 1986; Duncan, Gordon, & Scott, 1991). In a meta analysis on the effects of exercise on blood lipids in women, Lokey and Tran (1989) found exercise to be associated with an 8.8 mg/dL decrease in triglyceride level.

In a study on exercise and triglycerides in women, Cauley, Kriska, LaPorte, Sandler, and Pambianco (1986) randomized 229 postmenopausal women to a walking group or a control group for two years. The walking group showed no improvement in plasma triglyceride level. The total amount of exercise in the walking group, however, was not much different than the control group. The control group burned 1046.2 Kcal per week in physical activity at the end of the two years, whereas the walking group burned 1529.3

Kcal per week, which works out to less than 100 Kcal per day extra for the walking group. If an increase in physical activity does lead to lower triglycerides in women, the increased exercise in this study was not sufficient to stimulate this decrease.

In a cross sectional study, Gibbons, Blair, Cooper, & Smith (1983) performed maximal treadmill testing on 744 women aged 18-65. Cardiorespiratory fitness was significantly related to plasma triglyceride level, independent of age and weight. However, this study looked at both pre and post menopausal women, so this relationship might not hold true for postmenopausal women alone.

As with HDL cholesterol, there is little evidence supporting an improvement of triglyceride level in postmenopausal women due to increased exercise or an increased fitness level. An objective measure of cardiorespiratory fitness, in postmenopausal women, may tell us more about the relationship between triglycerides and exercise than just self reported physical activity.

Exercise and Fibrinogen

Leisure time physical activity and participation in recreational sports is inversely related to plasma fibrinogen level (Folsom, et al. 1991). Rankinen et al. (1993), in a cohort of 260 women aged 60-69, found a statistically significant inverse relationship between physical activity and plasma fibrinogen level. Stevenson, Davy, and Seals (1994), however, did not find a significant difference in fibrinogen levels between a group of postmenopausal endurance athletes and aged matched sedentary controls. This lack of a significant finding may be due to the small sample size, which included only 14 athletes and 17 sedentary controls. In addition, in the Stevenson et al., (1994) study the

blood sample was drawn 24 hours after the last exercise bout. It may be that the beneficial effects of exercise on fibrinogen are only an acute benefit from the latest exercise bout.

There is only minimal information on the association between physical activity and fibrinogen, especially in postmenopausal women. The current evidence however, points to lower levels of fibrinogen in those who are more physically active.

Exercise and Hormone Replacement Therapy

Two studies have been done on the combination of exercise and hormone replacement. Lindheim et al. (1994) examined the combined effects of exercise and hormone replacement therapy on blood lipid levels. Postmenopausal women (N=101) were randomly assigned to four groups: Sedentary control group (n=20), Exercise alone (n=25), Estrogen replacement using 0.625 mg per day of conjugated equine estrogen (n=28), and Exercise and Estrogen replacement (n=28). Exercise was performed on either a stationary bike or a treadmill and the participants exercised at approximately 70% of their maximum heart rate for 15 minutes 3 times a week. Following six months of follow up the exercise alone group significantly decreased their plasma levels of total cholesterol. They were also the only group to significantly decrease their triglycerides from 102.6 to 86.3 (19%). Those taking estrogen and not exercising significantly decreased their total cholesterol and increased their HDL cholesterol by 14% (60.8 to 69.5). In addition, they also showed a non significant increase in triglycerides. The combination group who took both unopposed estrogen replacement and exercised showed no change in total cholesterol. They increased their HDL cholesterol, but no further than

the group taking unopposed estrogen. Interestingly, the combination group also demonstrated a significant increase in triglycerides, from 102 to 142 mg/dL, whereas none of the other groups had a significant increase in triglycerides, also the exercise alone group showed a decrease in triglycerides. This finding is curious and hard to explain.

The lack of significant improvement in many of the blood values in the combination group, above the estrogen alone group may be partly related to the small size of the sample (less than 30 per group). The total amount of exercise in this study was also quite low, with exercising taking place only 3 days a week, for 15 minutes, at 70% of the participants maximum heart rate. This results in only 45 minutes at a moderate intensity of exercise per week.

More recently a similar randomized study of hormone replacement and exercise in 71 postmenopausal women was conducted. Subjects were divided into four groups: a control group; an exercise group; a hormone replacement group; and a combination group. In this study those taking hormone replacement, took estrogen in addition to progestin for 13 days per month, every third month. Exercise consisted of two months of low intensity exercise followed by nine months of exercise at 65-85% of maximal heart rate. Exercise was performed for 45 minutes per session, three or more days per week. The exercise group decreased their total cholesterol while showing no change in HDL cholesterol or triglycerides. The hormone replacement group increased their HDL cholesterol and triglycerides but had no change in total cholesterol. The combination group showed decreases in total cholesterol, and increases in HDL cholesterol, while showing no change in triglycerides (Binder, Birge, & Kohrt, 1996). This study differed

from the study by Lindheim et al., (1994) in that a greater amount of exercise was included and those on HRT took progestin in addition to estrogen, although the amount of progestin was less than what is normally taken in the general population.

Both of these studies examined the effects of HRT and exercise on blood lipid levels. To date no study has looked at the combined effects of exercise and HRT on other CVD risk factors such as fibrinogen in postmenopausal women. Also, no study has separately examined the effects of either unopposed estrogen, or a combination of estrogen and progestin when combined with exercise.

Summary

Elevated plasma levels of total cholesterol, triglycerides, and fibrinogen, and decreased levels of HDL cholesterol, are important risk factors for cardiovascular disease in postmenopausal women. Exercise and hormone replacement therapy have varying effects on each of these risk factors depending on the study population, the research methodology, and the risk factor measured. The precise direction and magnitude of the effect of exercise and hormone replacement is unclear in postmenopausal women.

Presently only two studies have examined the effects of a combination of exercise and hormone replacement on cardiovascular risk factors (Lindheim et al., 1994; Binder et al., 1996). No study has examined the effects of measured cardiorespiratory fitness in postmenopausal women while controlling for both estrogen and progestin replacement. Likewise, no study has looked at the relationship between measured cardiorespiratory fitness and blood clotting characteristics, such as fibrinogen, while controlling for hormone status, in postmenopausal women.

Research is needed to determine if increased levels of cardiorespiratory fitness has an effect on cardiovascular disease risk factors in postmenopausal women, while controlling for the effects of hormone replacement. If improved fitness does lead to an improvement in cardiovascular disease risk profile, knowing the degree of a change in fitness required to obtain positive benefits would be helpful in designing exercise programs for postmenopausal women.

CHAPTER 3: METHODS

Design

This study was a cross-sectional, retrospective analysis of the association between cardiorespiratory fitness and the cardiovascular disease risk factors of total cholesterol, HDL cholesterol, the total cholesterol/HDL cholesterol ratio, triglycerides, and fibrinogen.

Study Participants

The study participants were postmenopausal women who completed a preventive medicine physical exam at the Cooper Clinic in Dallas Texas, between 1987 and 1995. Data exist for early years, but prior to 1987 fibrinogen level was not recorded. Since fibrinogen is one of the key outcome variables being studied, data prior to 1987 were not included in this analysis.

Following is a list of the inclusion criteria for selection into this study. Participants were only included if they met the following criteria.

1. Postmenopausal women (a minimum of six months) who were patients of the Cooper Clinic between 1987 and 1995.
2. Completed a detailed questionnaire regarding their health and medication history at the time of their evaluation.
3. Blood analysis performed on the day of testing, with a minimum of 12 hours of fasting.
4. Completed a maximal, graded treadmill test, using a modified Balke protocol (Balke & Ware, 1959).

5. Reached a minimum of 85% of their age predicted maximal heart rate during treadmill testing, and not have been limited in performance by factors that could not be explained by aerobic fitness level, such as an orthopedic injury.
6. Non smokers. Subjects were considered to be smokers if they had smoked at any time in the previous two years. Smokers were not included in this analysis due to the effect of smoking on both blood lipid and fibrinogen levels.

Following the above inclusion criteria, records of 283 women were available for analysis. Many of the women included in this analysis came to the Cooper Clinic for testing on multiple occasions. In order to keep the data consistent we analyzed data from the first testing that took place for each participant during the study period (1987-1995).

Consent and Ethics

Prior to testing all subjects signed a written informed consent, allowing the data collected on them to be used for research. Each subject was given a seven digit ID, and information was recorded under that ID number, negating the need for name, thus assuring confidentiality. Permission for conducting this research was requested from the Institutional Review Board (IRB) of Loma Linda University on May 7, 1996, and granted on May 22, 1996. In addition, a formal letter of agreement was received from Steven Blair, P.E.D., of the Cooper Institute for Aerobics Research (CIAR) on May 15, 1996, giving permission to use their data in this research. The CIAR will be acknowledged on any and all publications produced from this research, along with the funding source (NIH AG06945). In addition Dr. Blair will be listed as a co-author on all publications.

Data Collection

All data were abstracted from a preexisting archival data base of the Cooper Institute for Aerobics Research (CIAR). This data base has been used in many other published research projects (Blair et al., 1996; Blair et al., 1993; Blair, Kohl, Barlow, & Gibbons, 1991; Blair, Kohl, Paffenbarger, Gibbons, & Macera, 1995; Blair, Kohl, Paffenbarger, Clark, Cooper, & Gibbons, 1989; Gibbons et al., 1983). Following is a list of each of the variables that were abstracted and how the information was collected:

1. Age - Collected from the computerized data base. The participants age was recorded as their age in years on the day of the examination.
2. Total treadmill time - Collected from the computerized data base. Treadmill was recorded as total time to volitional fatigue in seconds. Aerobic fitness level, or VO_2 max in ml O_2/kg/min, is often predicted based on an individual's total treadmill time to exhaustion and has been previously validated (Foster, et al., 1984; Pollock, Wilmore, & Fox, 1978). Subjects who did not meet the above mentioned inclusion criteria were coded as such and not included in this analysis.
3. Height - Collected from the computerized data base. Height was recorded to the nearest inch, and measured at the time of examination by a standard stadiometer.
4. Weight - Collected from the computerized data base. Height was recorded to the nearest pound, and measured on a standard physician's scale at the time of examination.
5. Body Mass Index (BMI) - Calculated from the height and weight, as the patient's weight in kg/m^2. Weight was converted from pounds to kilograms by dividing the

weight in pounds by 2.2. Height was converted from inches into meters by taking the height in inches times 0.0254.

6. Percent body fat by hydrostatic weighing - Collected from the computerized data base. Percent body fat was recorded to the nearest percent.
7. Percent body fat by skinfold measures - Collected from the computerized data base. Percent body fat was recorded to the nearest percent.
8. Alcohol intake - Collected from the computerized data base. Alcohol intake was based on a self report from the medical questionnaire, as the number of drinks per week.
9. Education - Abstracted from patient charts. Patients recorded the total number of years in formal education (i.e., A person who graduated from college with a bachelors degree would have 16 years of education).
10. Pregnancies - Collected from the computerized data base. Total number of pregnancies was based on patient self report on the medical questionnaire. This is the total number of pregnancies as opposed to the number of live births used in some research.
11. Blood Analysis - All blood analyses were performed following a minimum of 12 hours of fasting. Serum samples were analyzed by automated techniques in a laboratory participating in the Centers for Disease Control and Prevention Lipid Standardization Program (Blair et al., 1996).

A. Blood glucose - Abstracted from patient charts. Recorded in mg/dL, conversion of serum samples to mmol/L was accomplished by multiplying the reading in mg/dL by 0.05551.

B. Total cholesterol - Collected from the computerized data base, and recorded in mg/dL. Conversion to mmol/L was accomplished by multiplying the reading in mg/dL by 0.02586.

C. HDL cholesterol - Collected from the computerized data base, and recorded in mg/dL. Conversion to mmol/L was accomplished by multiplying the reading in mg/dL by 0.02586.

D. Total cholesterol/HDL cholesterol ratio - Calculated as the total cholesterol divided by the HDL cholesterol, and recorded to one significant digit past the decimal point.

E. Triglycerides - Collected from the computerized data base, and recorded in mg/dL. Conversion to mmol/L was accomplished by multiplying the reading in mg/dL by 0.01129.

F. Fibrinogen - Abstracted from patient charts, and recorded in mg/dL. Conversion to mmol/L was accomplished by multiplying the reading in mg/dL by 0.01.

12. Diabetes medication - Abstracted from patient charts. Patients were either classified as taking medication for controlling diabetes or not taking medication. For this analysis both use of insulin and oral medications were recorded as using diabetes medication.

13. Lipid lowering medication - Abstracted from patient charts. Patients were either classified as taking medication for reducing blood lipid levels or not taking this type of medication.
14. Personal history of diabetes - Abstracted from patient charts. Patients were classified as having a personal history of diabetes or no personal history of diabetes. For this analysis no distinction was made between those who were Type 1 vs. Type 2 diabetics.
15. Estrogen replacement - Abstracted from patient charts. Patients were classified by the use of estrogen. Due to the variety of types and dosages all subjects were collapsed into two groups: those taking estrogen replacement, or not taking estrogen replacement.
16. Progestin replacement - Abstracted from patient charts. Patients were classified by the use of progestin. Due to the variety of types and dosages all subjects were collapsed into two groups: those taking progestin replacement, or not taking progestin replacement.
17. Hysterectomy - Abstracted from the patient's chart. All patients were classified as either having had a hysterectomy or going through natural menopause.

Although fibrinogen was measured on some subjects, at the beginning of the data collection period, not all subjects had it measured and recorded. Therefore, the number of subjects available for analysis on measures of fibrinogen are lower than with the other outcome variables (n=162 vs. n=283).

Data Analysis

All data were abstracted from the original CIAR data set and patient records. Following collection, all data were entered into SPSS 7.0. Double entry was performed on 10% of the sample to assure accuracy, and no discrepancies were found. Descriptive statistics were run on all variables to check for outliers. One subject had a total cholesterol/HDL ratio of 21.5; and three subjects with fibrinogen values greater than 420. These outliers were removed from all relevant analysis since inclusion of these values skewed the data violating the normal curve assumption necessary for linear regression.

Cardiorespiratory fitness, as determined by total treadmill time to exhaustion, was used as the main predictor variable of the cardiovascular disease risk factors. Plasma levels of total cholesterol, HDL cholesterol, total cholesterol/HDL ratio, triglycerides, and fibrinogen were the outcome, or dependent, variables measured. Spearman correlations were used to determine if a linear relationship existed between measured cardiorespiratory fitness and the outcome variables. Linear regression was then used to determine the degree of variance in the outcome variables that could be accounted for by differences in cardiorespiratory fitness.

Subjects were divided by quintiles of cardiorespiratory fitness, based on the entire data set (Blair, et al., 1996, Blair et al., 1989). Approximately 46% of the subjects in this analysis were in the highest fitness quintile, instead of the expected 20%. This disproportionately large number in the highest quintile of fitness is most likely due to the exclusion of smokers in this analysis. T-tests were performed on all continuous variables to determine if significant differences existed between subjects in the highest fitness

category and those in the lower fitness categories. Similarly, Chi Square analysis was performed on categorical variables. An ANOVA was also performed to determine if significant differences existed between the different hormone replacement groups: those not taking hormone replacement, those taking unopposed estrogen, and those taking both estrogen and progestin. In addition, a two way ANOVA was performed to determine if there was an interaction between hormone replacement status and categorized fitness level (most fit quintile compared to all other subjects).

CHAPTER 4: PUBLISHIBLE PAPER

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CARDIORESPIRATORY FITNESS AND CARDIOVASCULAR DISEASE RISK FACTORS IN POSTMENOPAUSAL WOMEN

Authors: Bryan L. Haddock - Loma Linda University
Helen P. Hopp - Loma Linda University
Jenifer J. Mason - Loma Linda University
Glen Blix - Loma Linda University
Steven N. Blair - Cooper Institute for Aerobics Research

Corresponding Author: Bryan L. Haddock
Loma Linda University
Evans Hall #111
Loma Linda, CA 92350
(909) 478-8735
e-mail bHaddock@ccmail.llu.edu
Fax: (909) 824-4838

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CARDIORESPIRATORY FITNESS AND CARDIOVASCULAR DISEASE RISK FACTORS IN POSTMENOPAUSAL WOMEN

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Bryan L. Haddock	Helen Hopp
Jenifer Mason	Glen Blix
Steven N. Blair	

ABSTRACT

Objective: The purpose of the present study was to determine if individuals with high levels of cardiorespiratory fitness have better levels of the cardiovascular disease (CVD) risk factors of total cholesterol (TC), HDL cholesterol (HDL), total cholesterol/HDL cholesterol ratio (TC/HDL), triglycerides (TG), and fibrinogen (FIB), when compared with those with low fitness, in 283 nonsmoking, postmenopausal women. Second, we examined the relation between fitness and CVD risk after controlling for use of hormones and other possible confounding factors.

Methods: These analyses were done on a subset of non smoking, postmenopausal women in the Aerobics Center Longitudinal Study (ACLS). Records of postmenopausal women who completed a preventive medicine physical examination between 1987 and 1995, were examined. Cardiorespiratory fitness level was determined by total treadmill time to exhaustion on a graded exercise test; CVD risk factors were assessed via blood analysis.

Results: On cross sectional regression analysis, fitness was significantly associated ($p \leq 0.005$) with TC ($R^2 = .08$), TC/HDL ($R^2 = .12$), TG ($R^2 = .09$), and FIB ($R^2 = .06$), and an increase in HDL ($R^2 = .04$). After controlling for hormone status, age, year of testing, and blood glucose each outcome variable remained significantly associated with cardiorespiratory fitness ($p<0.05$). TC/HDL and TG continued to be significantly related to cardiorespiratory fitness after adjusting for body mass index (BMI) as a control variable ($p<0.01$). The lack of significance between TC, HDL, and FIB with

cardiorespiratory fitness, after adjusting for BMI, is likely due to the biological relationship between cardiorespiratory fitness and BMI ($R^2 = .19$).

Conclusions: We conclude that cardiorespiratory fitness is an important independent determinant of blood lipid and FIB levels in nonsmoking postmenopausal women, with or without HRT.

Key words: Hormone replacement, estrogen, progestin, blood lipids, fibrinogen.

INTRODUCTION

Paragraph Number 1 Prior to menopause women are at a decreased risk for cardiovascular disease (CVD) compared to men, with men having between 3.5 - 4.5 times the risk of women. Within 10 years following menopause the risk of CVD increases in women to a level similar to that seen in men (3,15).

Paragraph Number 2 Following menopause, significant changes occur in plasma lipids (14,20,28) and fibrinogen (FIB) (13,16,21,25). Hormone replacement, whether unopposed estrogen or a combination of estrogen and progestin, can have significant but mixed effects on CVD risk factors. Estrogen replacement in postmenopausal women is associated with a decrease in total cholesterol (TC), and an increase in HDL cholesterol (HDL) and triglycerides (TG). Depending on the dosage, the addition of progestin has been postulated to decrease both HDL and TG (19). The use of unopposed estrogen, or a combination of estrogen and progestin, also decreases the level of FIB (16,22).

Paragraph Number 3 Regular aerobic exercise and improvements in cardiorespiratory fitness increase HDL and decrease TG, while having no significant effect on TC (11). Increased aerobic exercise and improvements in cardiorespiratory fitness are also associated with decreases in FIB (12). Most research, however, on the association between exercise or fitness and these CVD risk factors has been done on men, and it is unclear if the benefits of improved cardiorespiratory fitness extend to women.

Paragraph Number 4 Both cardiorespiratory fitness and hormone replacement are thought to have a significant effect on CVD risk factors in postmenopausal women. To date no research has simultaneously examined the relation of cardiorespiratory fitness to

the CVD risk factors of TC, HDL, total cholesterol/HDL cholesterol ratio (TC/HDL), TG, and FIB, while controlling for hormone replacement, differentiating between unopposed estrogen and a combination of estrogen and progestin.

Paragraph Number 5 The purpose of this study was to determine if higher levels of cardiorespiratory fitness are associated with beneficial levels of TC, HDL, TC/HDL, TG, and FIB, in a group of nonsmoking, postmenopausal women. Second, we examined the relation between fitness and these CVD risk factors after controlling for hormone status and other possible confounding factors, including age, year of testing, blood glucose, and body mass index (BMI).

METHODS

STUDY PARTICIPANTS

Paragraph Number 6 The study participants were postmenopausal women who completed a preventive medical physical examination at the Cooper Clinic in Dallas Texas, between 1987 and 1995. All participants gave their written informed consent prior to participation in this study. In addition, this study was reviewed and approved by the Loma Linda University Institutional Review Board. Records of participants were included in our study if they reached at least 85% of their age-predicted maximum heart rate on their treadmill test, and were not limited by factors that could not be explained by their cardiorespiratory fitness, such as an orthopedic injury. Participants were excluded if they were current smokers or had quit smoking within the previous two years. In addition, all participants were free of known heart disease or cancer. Following the above exclusion criteria, there were 283 women available for data analysis.

DATA COLLECTION

Paragraph Number 7 All data were abstracted from the original Aerobics Center Longitudinal Study (ACLS) data files. Most of the data are in a computer data base in which patient information and testing results are entered following their physical examination. Information not included in the computer data base (hormone status, medication use, and surgical or natural menopause), was abstracted from patient charts. The clinical examination followed an overnight fast of at least 12 hours, and included a personal and family health history, a physical examination, a questionnaire on demographic characteristics and health habits, anthropemetry, resting ECG, blood chemistry analyses, blood pressure measurement, and a maximal exercise test using a standard protocol (2). Height and weight were measured on a standard physician's scale and stadiometer. BMI was calculated as the weight in kilograms divided by the square of height in meters. Blood pressures were measured by ausculatory methods with a mercury sphygmomanometer. Cardiorespiratory fitness was determined by total treadmill time to exhaustion. The protocol used in collecting these data has been shown to have a correlation with measured VO_2 max of 0.9 in women (23). Serum blood samples were analyzed by automated techniques in a laboratory participating in the Centers for Disease Control and Prevention Lipid Standardization Program.

Paragraph Number 8 Blood levels of fibrinogen were not measured on all subjects at the beginning of the data collection period; therefore the number of participants who had measures of fibrinogen was fewer than for the other outcome variables (n = 159 of 283, or 56%).

DATA ANALYSIS

Paragraph Number 9 All data were entered into SPSS 7.0 (27). Double entry was performed on 10% of the sample to check accuracy, and no discrepancies were found. Descriptive statistics were run on all variables to check for outliers. There was one outlier for the TC/HDL (21.5) and three outliers for FIB (465, 439, and 435 mg/dL); these subjects were removed from all relevant analyses since inclusion of these values skewed the data, violating the normal curve assumption necessary for linear regression.

Paragraph Number 10 Cardiorespiratory fitness, as determined by total treadmill time to exhaustion, was used as the main predictor variable for each of the CVD risk factors. Plasma levels of TC, HDL, TC/HDL, TG, and FIB were the CVD outcome variables measured. Participants were divided into quintiles of cardiorespiratory fitness based on their total treadmill time. Chi Square analyses and t tests were used to determine any differences between the upper and lower fitness groups. Spearman correlations were computed to determine if a linear relation existed between fitness and each of the five outcome variables. Linear regression was then used to determine the amount of variance in the CVD outcome variables that could be accounted for by cardiorespiratory fitness. Use of hormones, along with age, year of testing, blood glucose, and BMI were used as control variables to determine if an independent relationship existed between fitness and the CVD outcome variables. Other variables were not controlled for statistically due to their lack of contribution to outcome measures or the lack of significant difference found between the upper and lower fitness levels

(Table 1). Significance for all tests was set at a p value of ≤ 0.05, and adjusted for multiple comparisons using the Bonferoni technique.

RESULTS

Paragraph Number 11 Study sample characteristics are shown for all subjects in Table 1. Participants were divided into age adjusted quintiles based on the entire ACLS population (5-7). The subset of women in our study were more fit than the ACLS population as a whole. Instead of the expected 20% in each quintile, 131 (46%) of the sample fell into the highest fitness quintile. The main reason for this higher level of fitness is likely due to the use of only healthy nonsmokers in the present research. Previous research has divided the participants treadmill times into tertiles, comparing the lower 20%, the middle 40% and the upper 40% of fitness. Almost 50% of the subjects in this study were in the highest fitness quintile, and so this group of highly fit women were compared to the remainder of the subjects in our study (Table 1).

Paragraph Number 12 T-tests on the means of continuous variables showed significant differences between the upper and lower fitness levels for each of the outcome variables, along with significant differences in age, total treadmill time, height, weight, BMI, and percent fat based on hydrostatic and skinfold measures ($p < 0.01$). No significant differences were seen for blood glucose, amount of alcohol intake, years of education, or number of pregnancies. According to Chi Square analysis no significant differences existed between fitness levels on any of the categorical variables of medication use, history of diabetes, hormone replacement, or history of a hysterectomy. These variables were therefore not included in further analyses.

Paragraph Number 13 To examine the effect of hormone replacement on the five CVD outcome variables an ANOVA was performed for the three HRT groups (Table 2). The subjects taking no hormone replacement had a significantly lower HDL and a higher TC/HDL than those taking either unopposed estrogen or a combination of estrogen and progestin ($p \leq 0.001$). There were no other significant differences due to HRT. In order to assess if there was an interaction between hormone replacement, cardiorespiratory fitness and the CVD risk factors, a two-way ANOVA was performed. There was a significant interaction between hormone replacement and the upper and lower fitness level for TC/HDL ($F = 4.05$; $df = 5, 281$; $x = 4.0$; $p \leq 0.05$) (Figure 1). Higher fitness was associated with significantly lower TC/HDL in those who did not take hormone replacement (4.3 vs. 3.2) and those who took unopposed estrogen (3.5 vs. 3.0), but not in the group that took estrogen and progestin (3.3 vs. 3.0). No other two-way interactions were found, although a trend did occur with FIB ($p=0.10$).

Paragraph Number 14 Spearman correlations showed that total treadmill time was related linearly to each of the CVD outcome variables (Table 3). Regression analyses were then performed to determine the degree of variance in the outcome measures that could be accounted for by cardiorespiratory fitness. Cardiorespiratory fitness significantly predicted all CVD outcome variables (Table 4).

Paragraph Number 15 As seen in Table 4, cardiorespiratory fitness was significantly related to each of the outcome variables, independent of the effects of hormone replacement, age, year of testing, and blood glucose ($p<0.05$). Although blood glucose was not significantly different between the upper and lower fitness groups (Table

1), blood glucose was controlled for due to the association between blood glucose and diabetes, which effects blood lipid levels. Due to the strong association between cardiorespiratory fitness and BMI ($R^2 = .19$), regression analysis was performed on each outcome variable with and without BMI as a control. After controlling for BMI, in addition to hormone replacement, age, year of testing, and blood glucose, cardiorespiratory fitness continued to exert an independent effect on the TC/HDL and TG (Table 4).

DISCUSSION

Paragraph Number 16 To date only two studies have examined the combined effect of exercise and hormone replacement on blood lipids in postmenopausal women (4,17) (Table 5,6), while no research has examined the combined effect on FIB. Although both previous studies examined exercise and hormone replacement, the amount of exercise and the type of hormone replacement varied. Our study is cross sectional whereas the previous two studies were intervention studies. However, our study is the first to examine the effect of cardiorespiratory fitness on blood lipid and fibrinogen levels, while controlling for both unopposed estrogen or a combination of estrogen and progestin.

Paragraph Number 17 It is generally accepted that total cholesterol will not be reduced with an increase in exercise or with higher levels of fitness (11). In addition, research on postmenopausal women has failed to show this relationship (8,26,29), although two studies have shown a significant decrease in total cholesterol with exercise training (4,17). In our study, higher cardiorespiratory fitness was significantly associated with a lower TC ($p<0.001$, Table 4). This decrease in TC continued to be significant after

controlling for hormone replacement, age, year of testing, and blood glucose level ($p<0.005$, Table 4). Further study of cardiorespiratory fitness and total cholesterol, with diet as a covariate, would help determine if part of the difference is due to a better diet in more fit individuals.

Paragraph Number 18 HDL is expected to increase with increasing amounts of exercise, and increased cardiorespiratory fitness (11). Cross sectional studies of postmenopausal women tend to support this association between exercise and HDL (8,9). Follow up studies of exercise and HDL have not shown the same positive association in postmenopausal women (4,8,17). The use of an objective measure, such as cardiorespiratory fitness, probably led to the significant association found in our analyses (Table 4). A previous study of pre and post menopausal women did not show a significant improvement in HDL in those who started a jogging program compared to a control group, however, changes in endurance capacity were significantly associated with HDL (30). This discrepancy between the effects of cardiorespiratory fitness and exercise on HDL could be due to the amount and intensity of exercise performed. A study of older men and women found that exercise was only associated with an increase in HDL if the exercise was performed at greater than 80% of maximum heart rate (26).

Paragraph Number 19 Both TC and HDL are risk factors for CVD, and therefore the ratio of TC/HDL has been regarded as a significant indicator of CVD risk (18). Since cardiorespiratory fitness was significantly related to both TC and HDL, it was not surprising that the TC/HDL was significantly related to cardiorespiratory fitness in our

study ($p<0.001$, Table 4). Cardiorespiratory fitness accounted for 12% of the variance in the TC/HDL (Table 4).

Paragraph Number 20 The association between TG and CVD has been debated, however the evidence appears to point toward a positive association, especially in women (1). Previous research on the association between exercise and TG in postmenopausal women has shown mixed results, with some studies showing decreased TG with higher amounts of physical activity (17,29), whereas others have not demonstrated this relationship (4,8). Our study, however, indicates that higher levels of cardiorespiratory fitness are independently related to lower TG above the effect of age, year of testing, hormone status, blood glucose level and BMI (Table 4).

Paragraph Number 21 Exercise and increased cardiorespiratory fitness is thought to decrease FIB (12). Prior research specific to postmenopausal women has yielded mixed results with both a negative association (24) and no association (29). Our results support the hypothesis that increased cardiorespiratory fitness is associated with lower FIB ($p<0.005$, Table 5), with this association holding after controlling for hormone use, age, year of testing, and blood glucose ($p<0.05$, Table 5).

Paragraph Number 22 The significant association found in our research between cardiorespiratory fitness and each of the measured CVD risk factors is likely due to the use of an objective measure of cardiorespiratory fitness. Other studies have relied on self reported physical activity, which may fail to accurately reflect overall activity, whereas measured cardiorespiratory fitness accounts for both structured and unstructured exercise.

Paragraph Number 23 Hormone replacement is considered to have a strong influence on each of these CVD risk factors (16,19,22). Our research does point to a significantly higher HDL, and therefore a lower TC/HDL, in those who take either unopposed estrogen or a combination of estrogen and progestin compared to those who do not take hormone replacement. TC, TG, and FIB were not related significantly to the use of hormones, although TG tended to increase in those taking unopposed estrogen, while the addition of progestin tended to decrease the TG back toward what is seen in those not taking hormone replacement (Table 2). Our results indicate that cardiorespiratory fitness is more important than hormone replacement with respect to blood lipid and FIB levels, in that cardiorespiratory fitness was significantly related to the five CVD risk factors beyond the effect of hormone replacement (Table 4).

Paragraph Number 24 Cardiorespiratory fitness continued to be significantly related to each of the CVD risk factors except when controlling for BMI (Table 4). The drop in significance after controlling for BMI is expected since cardiorespiratory fitness is biologically related to body mass, with a decrease in body mass and fat being one of the mechanisms through which exercise and fitness exerts its effect (10). The fact that the TC/HDL ratio and TG were still significantly related to cardiorespiratory fitness, above and beyond the effects of BMI and the other control variables, indicates an even stronger relation for these two variables.

Paragraph Number 25 In summary, higher levels of cardiorespiratory fitness, as determined by maximal treadmill testing, were associated significantly with a lower TC, TC/HDL, TG, and FIB, and an increase in HDL in this group of non smoking,

postmenopausal women, on univariate analysis. Cardiorespiratory fitness was still associated significantly with each of the outcome variables after controlling for hormone replacement, age, year of testing, and blood glucose. The significant association with the TC/HDL, and TG continued to hold even after controlling for BMI. The current research provides strong evidence linking improved cardiorespiratory fitness with an improved CVD risk profile in non smoking, postmenopausal women, regardless of their hormonal status.

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Authors Addresses:

Bryan L. Haddock, Helen Hopp, Jenifer Mason, & Glen Blix
Loma Linda University
Nichol Hall #1511
Loma Linda, CA 92350

Steven N. Blair
The Cooper Institute for Aerobics Research
12330 Preston Rd.
Dallas, TX 75230

References

1. Austin, M.A., and J.E. Hokanson. Epidemiology of triglycerides, small dense low-density lipoprotein, and lipoprotein (a) as risk factors for coronary heart disease. *Medical Clinics of North Amer.* 78:99-115, 1994.

2. Balke, B., and R.W. Ware. An experimental study of physical fitness in air force personnel. *United States Armed Forces Medical Jour.* 10:675-688, 1959.

3. Barrett-Connor, E. Heart disease in women. *Fertility and Sterility.* 62(suppl):127s-132s, 1994.

4. Binder, E.F., S.J. Birge, and W.M. Kohrt. Effects of endurance exercise and hormone replacement therapy on serum lipids in older women. *Jour. of the American Geriatric Society.* 44:231-236, 1996.

5. Blair, S.N., J.B. Kampert, H.W. Kohl, C.E. Barlow, C.A. Macera, R.S. Paffenbarger, and L.W. Gibbons. Influences of cardiorespiratory fitness and other precursors on cardiovascular disease and all-cause mortality in men and women. *JAMA.* 276:205-210, 1996.

6. Blair, S.N., H.W. Kohl, C.E. Barlow, R.S. Paffenbarger, L.W. Gibbons, and C.A. Macera. Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men. *JAMA.* 273:1093-1098, 1995.

7. Blair, S.N., H.W. Kohl, R.S. Paffenbarger, D.G. Clark, K.H. Cooper, and L.W. Gibbons. Physical fitness and all-cause mortality. *JAMA.* 262:2395-2401, 1989.

8. Cauley, J.A., A.M. Kriska, R.E. Laporte, R.B. Sandler, and G. Pambianco. A 2-year randomized exercise trial in older women: Effects on HDL cholesterol. *Atherosclerosis.* 66:247-258, 1987.

9. Cauley, J.A., R.E. Laporte, R.B. Sandler, T.J. Orchard, C.W. Slemenda, and A.M. Petrini. The relationship of physical activity to high density lipoprotein cholesterol in postmenopausal women. *Jour. of Chronic Disease.* 39:687-697, 1986.

10. DiPietro, L. Physical activity, body weight, and adiposity: An epidemiologic perspective. *Ex. and Sports Sci. Rev.* 23:275-303, 1995.

11. Durstine, J.L., and W.L. Haskell. Effects of exercise training on plasma lipids and lipoproteins. *Ex. and Sports Sci. Rev.* 22:477-521, 1994.

12. Ernst, E. Regular exercise reduces fibrinogen levels: A review of longitudinal studies. *Brit. Jour. of Sports Med.* 27:175-176, 1993.

13. Folsom, A.R., K.K. Wu, C.E. Davis, M.G. Conlan, P.D. Sorlie, and M. Szklo. Population correlates of plasma fibrinogen and factor VII, putative cardiovascular risk factors. *Atherosclerosis.* 91:191-205, 1991.

14. Jensen, J. L. Nilas, L. and C. Christiansen. Influence of menopause on serum lipids and lipoproteins. *Maturitas.* 12:321-331, 1990.

15. Kafonek, S.D. Postmenopausal hormone replacement therapy and cardiovascular risk reduction: A review. *Drugs.* 27 suppl:16-24, 1994.

16. Lee, A.J., G.D.O. Lowe, W.C.S. Smith, and H. Tunstall-Pedoe. Plasma fibrinogen in women: Relationships with oral contraception, the menopause and hormone replacement therapy. *Brit. Jour. of Haematology.* 83:616-621, 1992.

17. 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.

18. Linn, S., R. Fulwood, M. Carroll, J.G. Brook, C.Johnson, W.D. Kalsbeek, and B.M. Rifkind. Serum total cholesterol/HDL cholesterol ratios in U.S. white and black adults by selected demographic and socioeconomic variables (NHANES II). *Am Jour. of Public Health.* 81:1038-1043, 1991.

19. Lobo, R.A. Clinical Review 27: Effects of hormonal replacement on lipids and lipoproteins in postmenopausal women. *Jour. of Clin. Endocrin. and Metab.* 73:925-930, 1991.

20. Matthews, K.A., E.N. Meilahn, L.H. Kuller, S.F. Kelsey, A.W. Caggiula, and R.R. Wing. Menopause and coronary heart disease. *New Eng. Jour. of Med.* 321:641-646, 1989.

21. Meade, T.W., A.P. Haines, J.D. Imeson, Y. Stirling, and S.G. Thompson. Menopausal status and haemostatic variables. *The Lancet.* 8:22-24, 1983.

22. Nabulsi, A.A., A.R. Folsom, A. White, W. Patsch, G. Haeiss, K.K. Wu, and M. Szklo. Association of hormone-replacement therapy with various cardiovascular risk factors in postmenopausal women. *New Eng. Jour. of Med.* 328:1069-1075, 1993.

23. Pollock, M.L., R.L. Bohannon, K.H. Cooper, J.J. Ayres, Ward., S.R. White, and A.C. Linnerud. A comparative analysis of four protocols for maximal treadmill stress testing. *Amer. Heart Jour.* 92:39-46, 1976.

24. Rankinen, T., R. Rauramaa, S. Vaisanen, I. Penttila, S. Saarikoski, J. Tuomilehto, and A. Nissinen. Inverse relationship between physical activity and plasma fibrinogen in postmenopausal women. *Atherosclerosis.* 102:181-186, 1993.

25. Scarabin, P., G. Plu-Bureau, L. Bara, C. Bonithon-Kopp, L. Guize, and M.M. Samama. Haemostatic variables and menopausal status: Influence of hormone replacement therapy. *Thromb. and Haemostasis.* 70:584-587, 1993.

26. Seals, D.R., J.M. Hagberg, B.F. Hurley, A.A. Ehsani, and J.O. Holloszy. Effects of endurance training on glucose tolerance and plasma lipid levels in older men and women. *JAMA.* 252:645-649, 1984.

27. SPSS for Windows. Release 7.0 (Dec. 19, 1995). Copyright SPSS Inc., 1989-1995.

28. Stevenson, J.C., D. Crook, and I.F. Godsland. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis.* 35:277-286, 1993.

29. Stevenson, E.T., K.P. Davy, and D.R. Seals. Hemostatic, metabolic, and androgenic risk factors for coronary heart disease in physically active and less active postmenopausal women. *Arter. Thromb. and Vasc. Biol.* 15:669-677, 1994.

30. Suter, E., and B. Marti. Little effect of long term, self monitored exercise on serum lipid levels in middle aged women. *Jour. of Sports Med. and Phys. Fit.* 32:400-411, 1992.

Table 1: Subject Characteristics

Characteristics	N	Total X (SD) or %	Quintiles 1-4 X (SD) or %	Quintile 5 X (SD) or %
Age	283	53.0 (7.1)	53.3 (7.4)	52.6 (6.7)
Total treadmill time (seconds)	283	815.1 (261.7)	633.7 (154.3)	1025.4 (194.7)*
Height (inches)	283	64.6 (2.3)	64.4 (2.4)	64.8 (2.2)
Weight (lb.)	283	137.5 (24.3)	144.3 (28.2)	129.6 (15.4)*
Body mass index (kg/m^2)	283	23.2 (4.0)	24.5 (4.6)	21.7 (2.4)*
Percent fat (hydrostatic weighing)	271	30.8 (7.4)	34.1 (6.7)	26.8 (6.2)*
Percent fat (skinfold measures)	282	28.1 (6.2)	30.9 (5.6)	24.9 (5.2)*
Number of alcohol drinks/week	283	3.0 (4.4)	2.8 (4.6)	3.3 (4.1)
Years of education	261	15.2 (2.2)	15.1 (2.3)	15.3 (2.2)
Number of pregnancies	283	2.9 (1.8)	2.8 (1.9)	2.9 (1.8)
Fasting glucose mg/dL mmol/L	270	96.2(24.9) 5.3 (1.4)	97.5 (27.0) 5.4 (1.5)	94.6(21.9) 5.3(1.2)

Cholesterol mg/dL	282	217.1(40.4)	224.4(40.3)	208.3(39.0)*
mmol/L		5.6(1.0)	5.8(1.0)	5.4(1.0)
HDL-C mg/dL	282	66.8(16.7)	64.5(16.3)	70.0(16.1)
mmol/L		1.7(0.4)	1.7(0.4)	1.8(0.4)
TC/HDL cholesterol	282	3.5 (1.5)	3.7 (1.2)	3.1 (0.9)*
Triglycerides mg/dL	283	101.8(67.8)	114.4(74.8)	87.1(55.3)*
mmol/L		1.5(0.8)	1.3(0.8)	1.0(0.6)
Fibrinogen mg/dL	159	260.0(51.3)	265.2(46.9)	245.4(39.7)
g/L		2.6(0.5)	2.7(0.5)	2.5(0.4)
Lipid lowering drugs	283	5.3%	7.2%	3.1%
History of diabetes	283	2.1%	2.6%	1.5%
Diabetes medication	283	1.8%	2.0%	1.5%
Unopposed Estrogen	283	39.9%	38.2%	42.0%
Estrogen & Progestin replacement	283	20.8%	19.7%	22.1%
Hysterectomy	283	58%	57.9%	58.0%

Data are given as means and (standard deviations) for all continuous variables, and percentages for categorical variables. Significance levels are based on t-tests between means, and χ^2 for frequencies, between upper and lower fitness categories. HDL-C and Fibrinogen were significant at a $p<0.01$ prior to Bonferoni adjustment.

* = $p<0.001$.

Table 2: Hormone Replacement Therapy and Cardiovascular Disease Risk Factors

Variable	N	No HRT (N = 110)	Unopposed Estrogen (N = 113)	Estrogen and Progestin (N = 59)	F - value
Total cholesterol	282	219.9 (41.7)	217.5 (43.0)	210.7 (32.2)	1.00
HDL cholesterol	282	61.8 (17.2)	70.7 (15.6)	69.7 (13.8)	9.86*
Total cholesterol/HDL ratio	282	3.8 (1.2)	3.2 (1.0)	3.1 (0.8)	11.13*
Triglycerides	283	95.3 (66.3)	111.4 (79.1)	95.5 (39.9)	1.92
Fibrinogen	159	260.1 (47.9)	258.1 (45.7)	249.0 (38.9)	0.80

Data are given as means and (standard deviations). The F value is for a one way ANOVA between the three HRT groups. * = $p<0.001$ According to post hoc analysis, using paired t-tests the significant differences occur between the no HRT group and both of the two groups taking some form of hormone replacement. No significant differences occur between the two groups taking hormone replacement.

Table 3: Correlation Between Total Treadmill Time and CVD Outcome Variables

Variable	Spearman's r
Total cholesterol	-0.32†
HDL cholesterol	0.18*
Total cholesterol/HDL cholesterol ratio	-0.35†
Triglycerides	-0.32†
Fibrinogen	-0.25*

Results are based on Spearman correlations. * = $p<0.005$. † = $p<0.001$

Table 4: Cardiorespiratory Fitness and Outcome Variables

Variable	N	βeta	Total R^2	R^2 above control variables	R^2 above control variables, except BMI	R^2 above BMI only
Total Cholesterol	282	-.285	.08‡‡	.01	.03‡	.05‡‡
HDL Cholesterol	282	.198	.04‡‡	.01	.04‡‡	.004
Total Cholesterol / HDL Ratio	282	-.347	.12‡‡	.02†	.08‡‡	.03‡
Triglycerides	283	-.306	.09‡‡	.02†	.07‡‡	.03‡
Fibrinogen	159	-.240	.06‡	.02	.03*	.03*

Values given are the R^2 for the listed variables with the total treadmill time in seconds as the independent variable. Total R^2 is for total treadmill time, without control for any other factors. Control variables include hormone replacement, age, year of testing, blood glucose, and body mass index. * = $p<0.05$. † = $p<0.01$. ‡ = $p<0.005$. ‡‡ = $p<0.001$

Table 5: A Comparison of Two Studies on Exercise and Hormone Replacement

	Lindheim et al., 1994	**Binder, Birge, & Kohrt, 1996**
Four study groups	Unopposed Estrogen, Exercise, Estrogen & Exercise, Control	Estrogen/Progestin, Exercise, Exercise & Estrogen/Progestin, Control
Number of participants	101: 20-28 per group	71: Less than 20 per group
Length of follow up	6 months	11 months (9 months of aerobic exercise)
Intensity of aerobic exercise	70% of maximum H.R.	70-85% of maximum H.R.
Duration of aerobic exercise per session	15 minutes	45 minutes
Frequency of aerobic exercise	3 days	3 or more days
Hormone replacement	Daily estrogen	Daily estrogen, 13 days of progestin every third month

Table 6: Results of Studies on Exercise and Hormone Replacement

	Lindheim et al. 1994			Binder, Birge, Kohrt, 1996		
	Exercise	Estrogen	Both	Exercise	Est/Prog	Both
Total Cholesterol	-6%*	-5%*	-2%	-6%†	-2%	-6%*
HDL Cholesterol	NC	+14%‡	+12%†	NC	+21%†	+17%†
Triglycerides	-16%*	+5%	+40%†	-8%	+42%†	+2%

The percent change from baseline is listed for each group, in both studies

* = $p<0.05$, † = $p<0.01$, ‡ = $p<0.001$, NC = No change from baseline

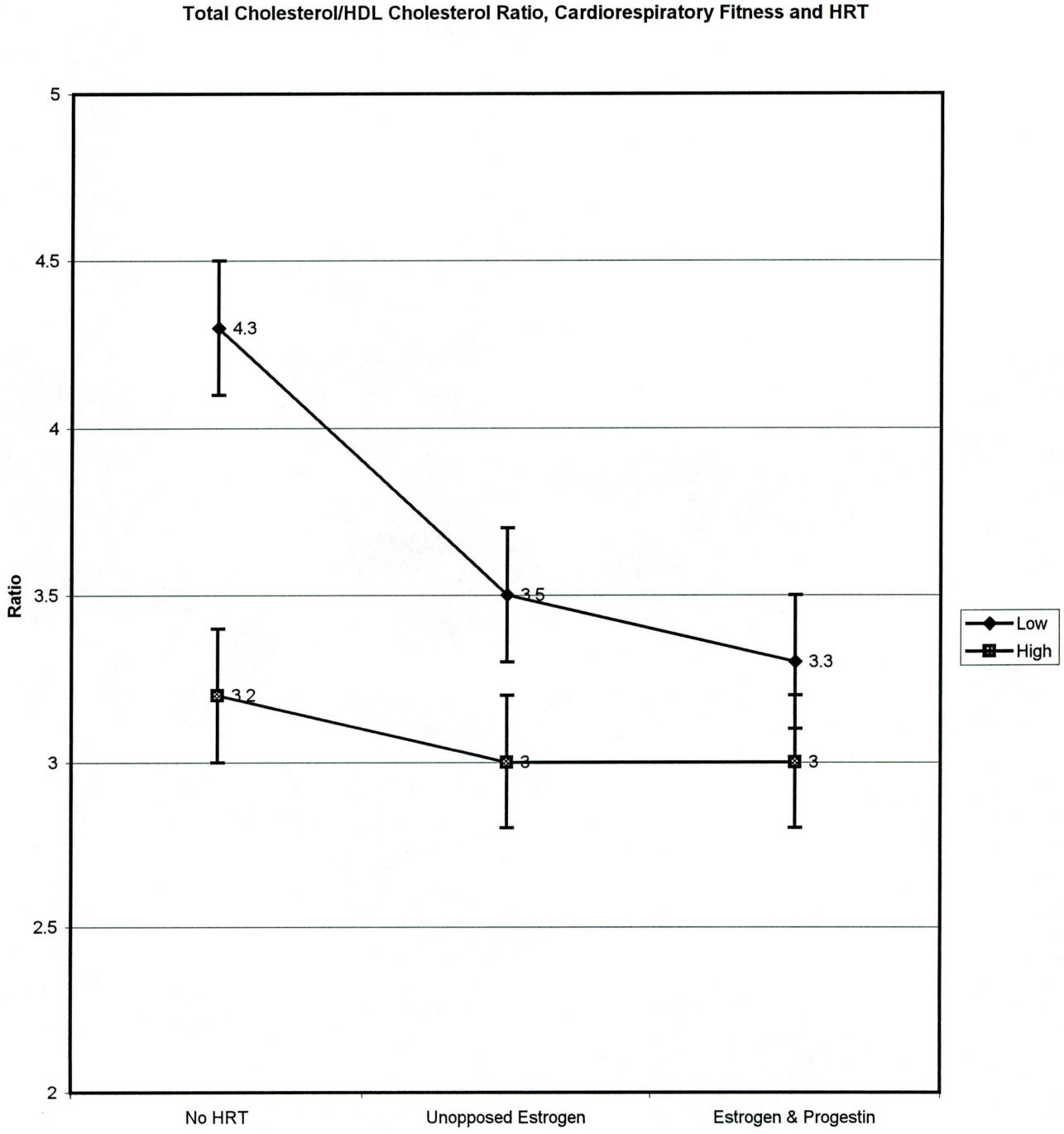


Figure 1: The Total cholesterol/HDL cholesterol ratio by fitness status and hormone status. High fitness denotes fitness in the highest quintile. All others are deonted by low fitness. A two way ANOVA shows a significant interaction ($p<0.05$)

CHAPTER 5: OTHER FINDINGS

Introduction

In the article, earlier in this document, there was not adequate space to address all of the findings of this study. This section will expand on some of the findings reported in the article, and present new results.

Fitness and Individual Control Variables

According to the Spearman correlations, cardiorespiratory fitness based on total treadmill time, was significantly related to each of the outcome variables ($p = < 0.005$). Measured cardiorespiratory fitness was also significantly correlated to age, number of alcohol drinks per week, height, weight, body mass index, and percent body fat based on both hydrostatic weighing and skinfold measures (Table 5.1). However, following Bonferoni adjustment alcohol drinks per wee, height, HDL cholesterol, and fibrinogen were no longer significantly related to cardiorespiratory fitness.

Table 5.1 Correlation Between Cardiorespiratory Fitness and Other Variables

Variable	N	Correlation
Age	283	-.36‡
Alcohol drinks per week	283	.17†
Total years of education	259	.11
Total number of pregnancies	281	-.05
Height	283	.15*
Weight	283	-.37‡
Body mass index	283	-.46‡
Percent fat based on hydrostatic weighing	270	-.62‡
Percent fat based on skinfold measures	281	-.59‡
Blood glucose	267	-.10
Total cholesterol	282	-.30‡
HDL cholesterol	282	.19†
Total cholesterol/HDL ratio	282	-.35‡
Triglycerides	283	-.33‡
Fibrinogen	158	-.25†

*= $p<0.05$, †= $p<0.005$, ‡= $p<.001$.

Fitness and Measures of Excess Weight

The strongest correlations were found between cardiorespiratory fitness and the three measures of excess weight: body mass index ($r = -0.46$, $p<0.001$), percent fat based on skinfold measures ($r = -0.59$, $p<0.001$), and percent fat based on hydrostatic weighing ($r = -0.62$, $p<0.001$). In addition, these measures of excess weight were significantly related to each of the outcome variables (Table 5.2).

Table 5.2 Correlations Between Measures of Excess Weight and the Outcome Variables

	N	BMI	Percent fat based on skinfold measures	Percent fat based on hydrostatic weighing
Total cholesterol	289	.25‡	.33‡	.33‡
HDL cholesterol	289	-.27‡	.-.23‡	-.24‡
Total cholesterol/HDL ratio	289	.37‡	.39‡	.42‡
Triglycerides	289	.36‡	.41‡	.32‡
Fibrinogen	183	.19*	.23†	.31‡

*= $p<0.05$, †= $p<0.005$, ‡= $p<.001$

Since cardiorespiratory fitness was significantly related to each of the measures of excess weight, and these same measures of excess weight are significantly related to each of the outcome variables, the ability of cardiorespiratory fitness to predict the outcome measures would be reduced when controlling for these measures of excess weight. According to linear regression analysis, measured cardiorespiratory fitness significantly predicted each of the outcome variables ($p<0.005$): R^2 for total cholesterol = .08, R^2 for HDL cholesterol = .04, R^2 for the total cholesterol/HDL ratio = .12, R^2 for triglycerides = .09, and R^2 for fibrinogen was .06. In Table 5.3 the R^2 for cardiorespiratory fitness is given for the amount of variance predicted above what can be accounted for by individual control variables. The R^2 is decreased for each variable when controlling for measures of

excess weight, and in some cases the cardiorespiratory fitness is no longer significantly associated with the outcome variable. This indicates that a large part of the effect of cardiorespiratory fitness on the outcome variables is mediated through its effect on body composition. Other control variables may decrease the R^2 for fitness, but fitness still significantly predicted each.

Table 5.3 R^2 for Fitness Above the Effects of Control Variables.

Control variable	Total cholesterol	HDL cholesterol	Total cholesterol/ HDL ratio	Triglycerides	Fibrinogen
Age	.03‡‡	.04‡‡	.09‡‡	.07‡‡	.03‡‡
Years of education	.09‡‡	.04‡‡	.13‡‡	.09‡‡	.05*
Number of pregnancies	.08‡‡	.04‡‡	.12‡‡	.09‡‡	.05‡
Alcohol drinks per week	.08‡‡	.04‡	.11‡‡	.10‡‡	.05‡
Height	.07‡‡	.04‡	.10‡‡	.09‡‡	.05‡
Weight	.07‡‡	.01	.05‡‡	.04‡‡	.04*
Body mass index	.05‡‡	.00	.03‡	.03‡	.03*
Percent body fat based on skinfold measures	.02*	.01	.02†	.01*	.02
Percent body fat based on hydrostatic weighing	.01	.01	.01	.02*	.00
Blood glucose	.08‡‡	.04‡‡	.11‡‡	.09‡‡	.05‡
History of a hysterectomy	.08‡‡	.04‡‡	.12‡‡	.10‡‡	.06‡
Estrogen replacement	.08‡‡	.03‡	.11‡‡	.10‡‡	.06‡
Progestin replacement	.08‡‡	.04‡‡	.12‡‡	.09‡‡	.06‡

*= $p<0.05$, †= $p<0.01$, ‡= $p<0.005$, ‡‡= $p<0.001$

As would be expected, based on the above discussion, measures of excess weight, regardless of how it was measured, significantly predicted each of the outcome variables on regression analysis (Table 5.4).

Table 5.4 R^2 for Measures of Excess Weight

Variable	Body mass index	Percent body fat based on skinfold measures	Percent body fat based on hydrostatic weighing
Total cholesterol	.04†	.09‡	.10‡
HDL cholesterol	.10‡	.06‡	.08‡
Total cholesterol/HDL ratio	.18‡	.16‡	.19‡
Triglycerides	.11‡	.14‡	.09‡
Fibrinogen	.04*	.03*	.08‡

*= p<0.05, †= p<0.005, ‡= p<.001.

As shown in Table 5.5, controlling for cardiorespiratory fitness reduces the R^2 for excess weight in each case, just as controlling for excess weight decreased the R^2 for fitness (Table 5.4). Cardiorespiratory fitness and obesity, or excess weight, are biologically related. Therefore, caution must be applied when controlling for both in a single analysis. The decrease in statistical significance could mask the true effect of the independent variable on the outcome.

Table 5.5 R^2 for Measures of Excess Weight, Controlling for Fitness.

Variable	Body mass index	Percent body fat based on skinfold measures	Percent body fat based on hydrostatic weighing
Total cholesterol	.01	.03†	.03†
HDL cholesterol	.06‡	.02*	.03†
Total cholesterol/HDL ratio	.09‡	.05‡	.07‡
Triglycerides	.04‡	.05‡	.02*
Fibrinogen	.01	.00	.04*

*= p<0.05, †= p<0.005, ‡= p<.001.

It appears that much of the effect of higher cardiorespiratory fitness on the outcome variables is mediated through its effect of excess weight. Cardiorespiratory fitness was still significantly related to the total cholesterol/HDL cholesterol ratio and triglycerides above the effects BMI and other control variables, including hormone replacement, age, year of testing, and blood glucose.

Fitness Quintiles and Outcome Variables

Previous research conducted using the data from the CIAR has typically used quintiles of fitness to determine if cardiorespiratory fitness was related to the outcomes, primarily mortality (Blair et al., 1989; Blair et al., 1996). One advantage of using fitness quintiles is that it can be determined if differences in outcomes come equally between each of the quintile groups or if the majority of difference occurs between certain groups. Using the same cutoff points as in the previous research, there were significant differences between the five groups based on an ANOVA (Table 5.6). This significant finding occurred in spite of the fact that there were many more subjects in the highest fitness category (46%) than in each of the lower fitness categories.

Table 5.6 ANOVA's with Quintiles Used in Previous Research

Means and (N)

Variable	1 (N)	2 (N)	3 (N)	4 (N)	5(N)	F
Total cholesterol	218(13)	239(30)	213(40)	226(69)	208(130)	4.94†
HDL cholesterol	59(13)	65(30)	60(40)	68(69)	70(130)	4.01†
Total cholesterol/HDL ratio	4.0(13)	3.9(30)	3.8(40)	3.5(69)	3.1(130)	6.61‡
Triglycerides	146(13)	139(30)	107(40)	102(69)	87(131)	5.53‡
Fibrinogen	264(6)	265(17)	251(26)	275(39)	245 (70)	3.15*

*= $p<0.05$, †= $p<0.005$, ‡= $p<.001$

Note: For total cholesterol significant differences occurred between the following groups: 2 vs. 5, and 4 vs. 5. For HDL cholesterol significant differences occurred between the following groups: 3 vs. 5. For the Total cholesterol/HDL ratio significant differences occurred between the following groups: 1 vs. 5, 2 vs. 5, and 3 vs. 5, For triglycerides significant differences occurred between the following groups: 1 vs. 5, and 2 vs. 5. For fibrinogen significant differences occurred between the following groups: 4 vs. 5.

The lack of significant differences between some of the individual groups could be due to the low number of subjects in some of the quintiles, especially the lowest fitness quintile. However, the total cholesterol/HDL cholesterol ratio and triglycerides show a negative linear trend through the quintiles, with each higher level of fitness showing a lower value than the previous quintile. In addition, in each outcome the highest fitness group had a significantly better value than at least one of the lower fitness groups.

Since use of the previous research cutoff points yield a disproportionate number of subjects in the high fitness category a straight quintile split was done on just the subjects in this study. The groups are not exactly equal due to multiple subjects having the same total time on the treadmill. As was the case when using the previous cutoff points each outcome variable varied significantly across fitness levels with those in higher fitness quintiles demonstrating a better cardiovascular disease risk profile (Table 5.7).

Table 5.7 ANOVA's with Quintiles Using a Straight Cut Off for Treadmill Times Means and (N)

Variable	1	2	3	4	5	F
Total cholesterol	232(47)	227(62)	218(59)	208(57)	202(57)	5.37†
HDL cholesterol	61(47)	64(62)	69(59)	69(57)	70(57)	3.176*
Total cholesterol/HDL ratio	4.1(47)	3.7(62)	3.3(59)	3.1(57)	3.0(57)	9.635†
Triglycerides	139(47)	119(62)	95(59)	79(58)	82(57)	8.242†
Fibrinogen	274(28)	263(33)	253(36)	251(29)	242(32)	2.35

*= $p<0.05$, †= $p<0.001$

Note: For total cholesterol significant differences occurred between 1 vs. 4, 1 vs. 5, and 2 vs. 5. For HDL cholesterol significant differences occurred between 1 vs. 5. For the ratio significant differences occurred between 1 vs. 3, 1 vs. 4, 1 vs. 5, 2 vs. 4, and 2 vs. 5. For triglycerides significant differences occurred between 1 vs. 3, 1 vs. 4, 1 vs. 5, 2 vs. 4, and 2 vs. 5.

Post hoc analysis revealed where the significant differences fell. In the straight quintile split all significant differences were between those in the two lowest categories and one or more of the upper three categories. Therefore, once reaching the third quintile or moderate fitness level, there are no significant differences between that level and the top fitness levels. However, the highest fitness group had significantly better values on each outcome variable, compared to at least one of the lower fitness groups.

Fitness and HRT

In all cases, except for total cholesterol, the correlation between measured cardiorespiratory fitness and the outcome variables was the greatest in those not taking any hormone replacement. In total cholesterol the highest correlation was found in those taking both estrogen and progestin (r =.29) however the correlation with those taking no hormone replacement was just slightly lower (r =.28), and the p value was greater in those not taking any hormone replacement, probably due to a higher N (Table 5.8).

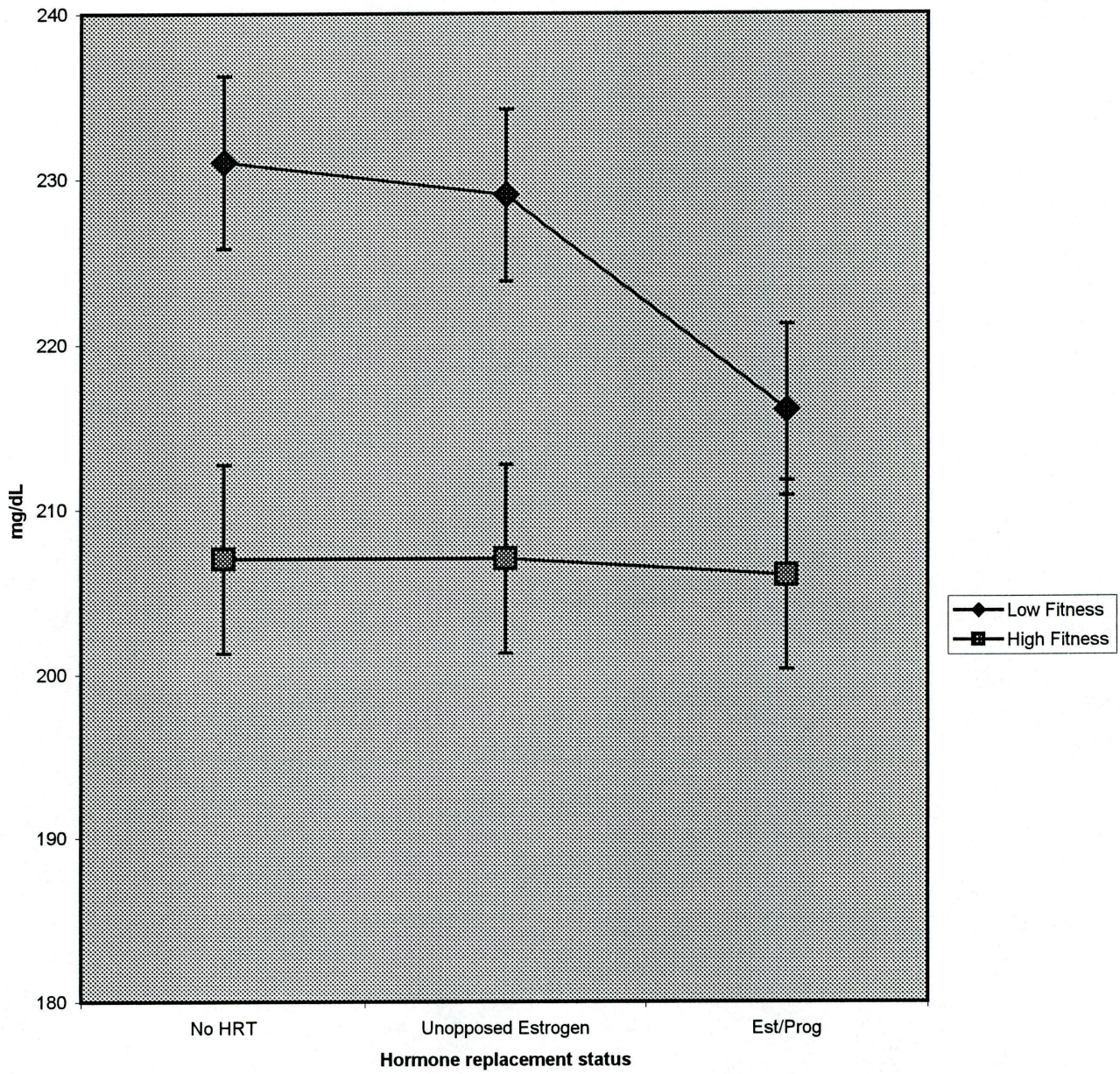
Table 5.8 Correlation's Between Treadmill Time and the Outcome Variables in Each of the HRT Groups r (N)

Variable	No hormone use (N)	Estrogen only (N)	Estrogen and Progestin (N)
Total cholesterol	-.28‡(110)	-.26†(113)	-.29*(59)
HDL cholesterol	.27†(110)	.10(113)	.10 (59)
Total cholesterol/HDL ratio	-.44‡‡(110)	-.26†(113)	-.21 (59)
Triglycerides	-.40‡‡(111)	-.29‡(113)	-.33*(59)
Fibrinogen	-.30*(55)	-.21(62)	-.21(41)

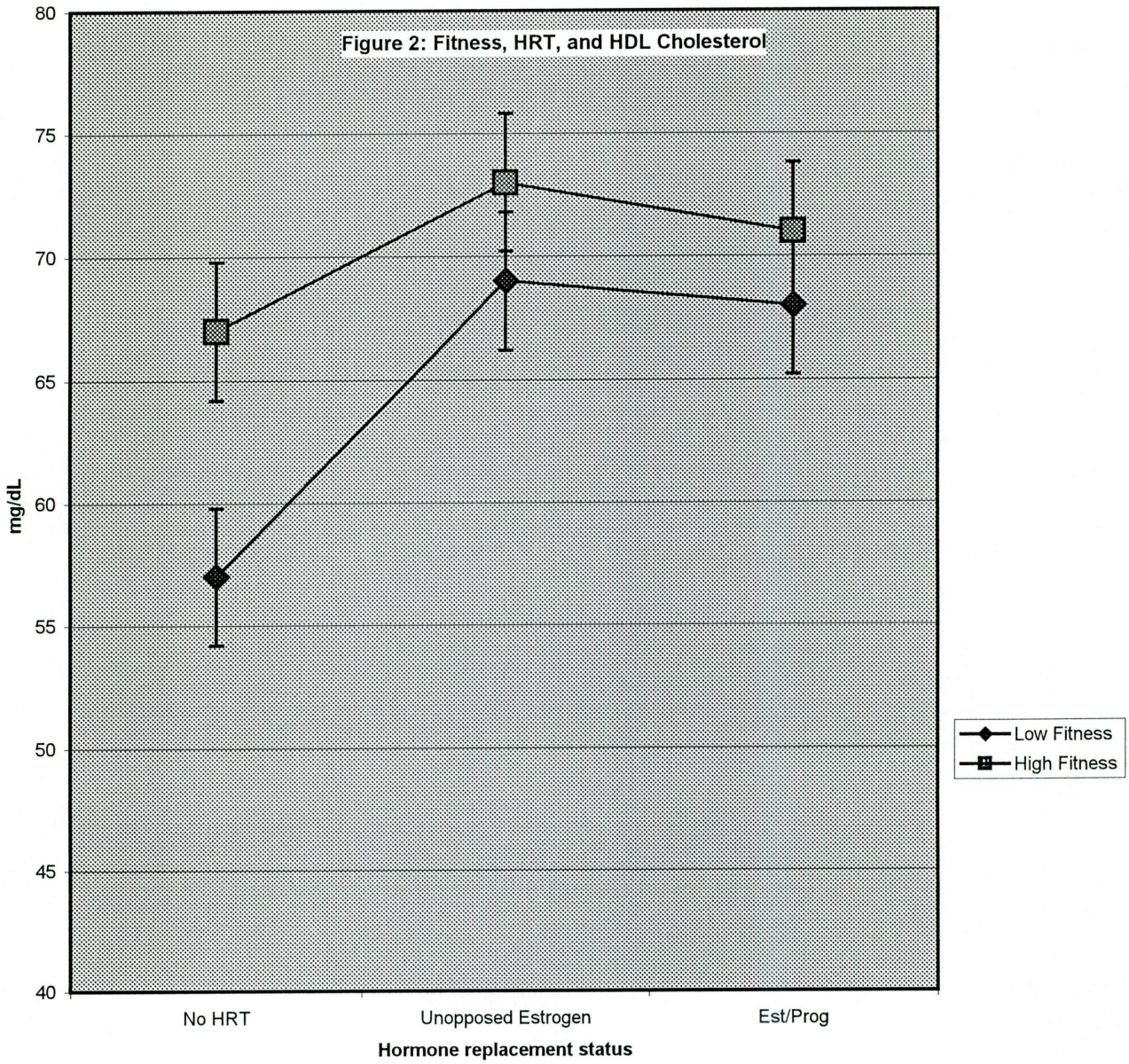
*= $p<0.05$, † = $p<0.01$, ‡ = $p<0.005$, ‡‡ = $p<0.001$

In order to determine if there was an interaction between fitness and hormone status a 2-way ANOVA was performed on each of the outcome variables (Figure:5.1-5). Although it appears that a greater difference exists between the high and low fitness groups in those not taking hormone replacement, the only statistically significant interaction was found with the total cholesterol/HDL cholesterol ratio ($p<0.05$). Fibrinogen did show a trend toward and interaction however ($p=0.10$). Perhaps with a greater number of subjects in each group a significant interaction would have been seen in fibrinogen and the other groups.

Figure 1: Fitness, HRT, and Total Cholesterol

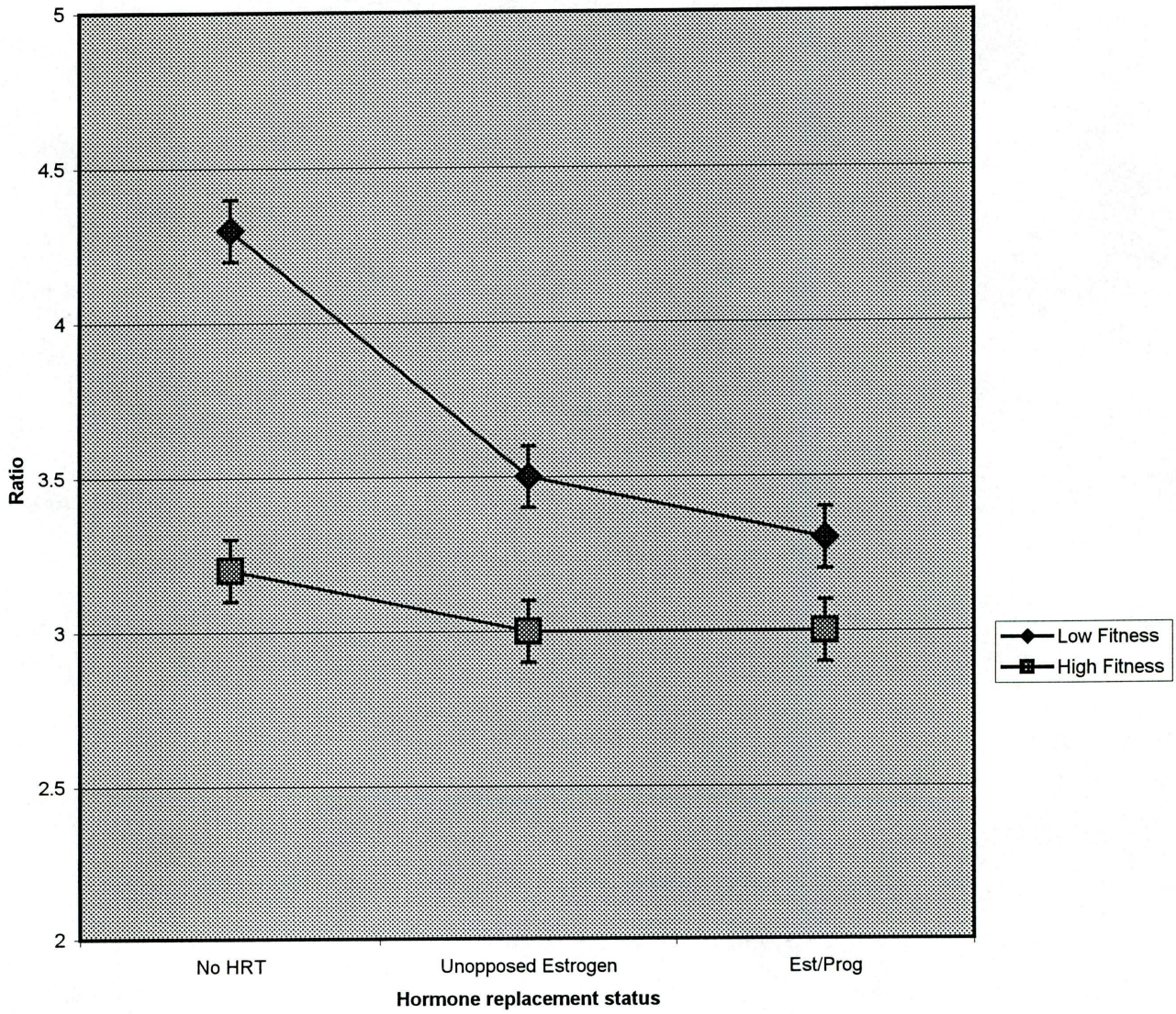


The mean values for total cholesterol are listed for the highest fitness quintile and all others for each of the hormone replacement groups. On 2-way ANOVA no significant interactions were observed.



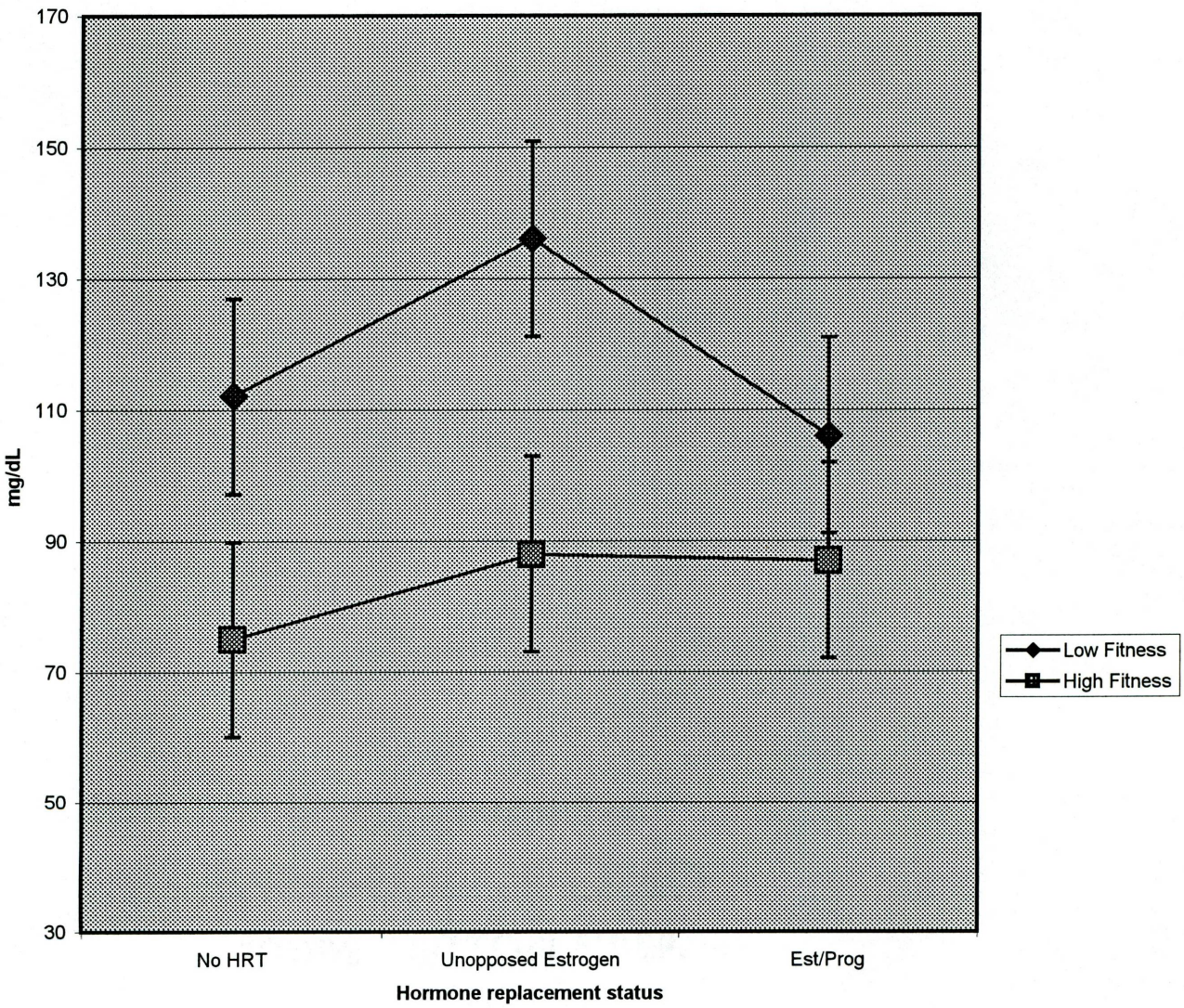
The mean values for HDL cholesterol are listed for the highest fitness quintile and all others for each of the hormone replacement groups. On 2-way ANOVA no significant interactions were observed.

Figure 3: Fitness, HRT, and the Total Cholesterol/HDL Cholesterol Ratio



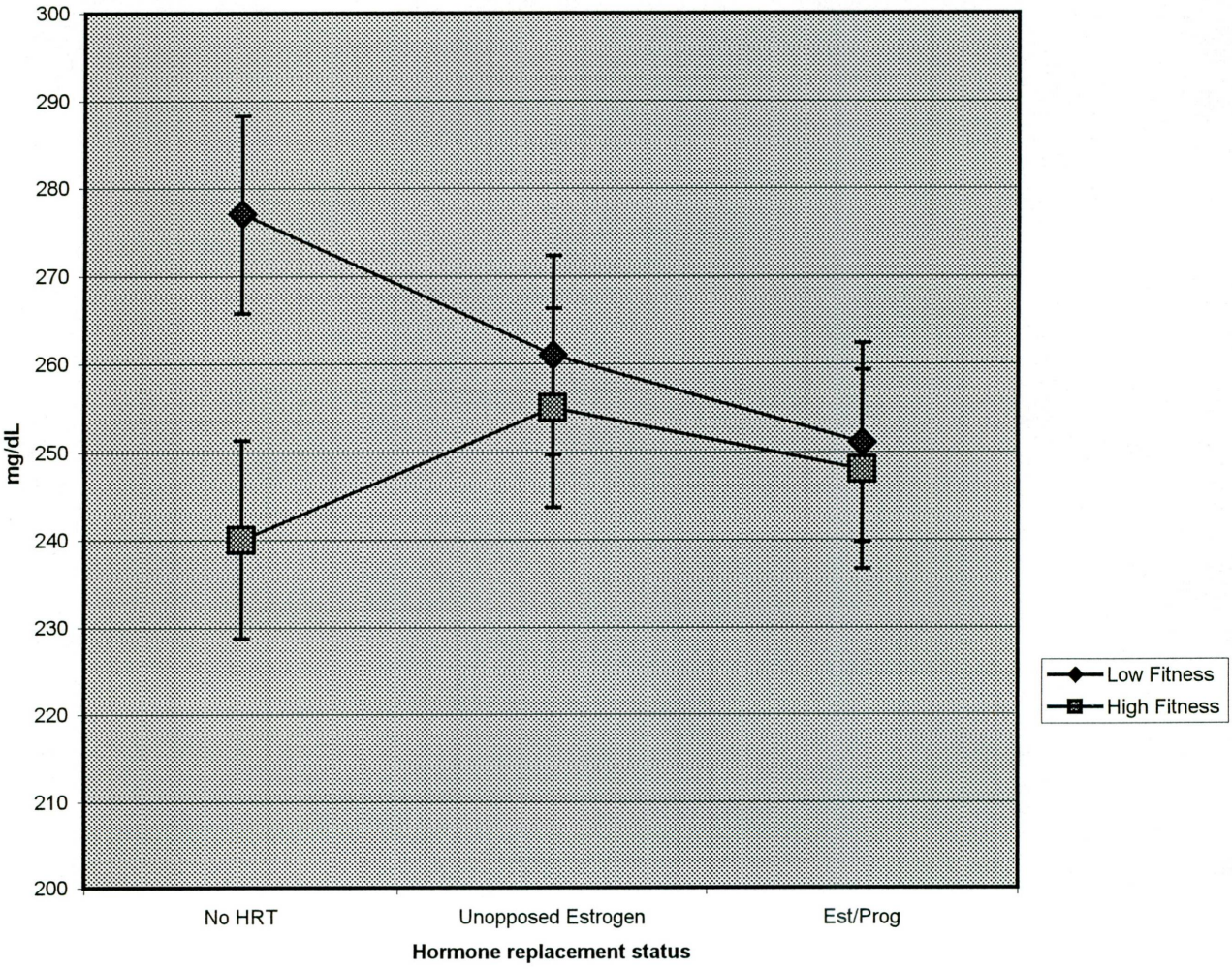
The ratio is listed for the highest fitness quintile and all others for each of the hormone replacement groups. On 2-way ANOVA a significant interaction was observed.

Figure 4: Fitness, HRT, and Triglycerides



The mean values for triglycerides are listed for the highest fitness quintile and all others for each of the hormone replacement groups. On 2-way ANOVA no significant interactions were observed.

Figure 5: Fitness, HRT, and Fibrinogen



The mean values for Fibrinogen are listed for the highest fitness quintile and all others for each of the hormone replacement groups. On 2-way ANOVA no significant interactions were observed.

CHAPTER 6: STRENGTHS AND LIMITATIONS OF THIS RESEARCH

Strengths

As with all research, this study had both strengths and weaknesses. This study was not able to answer all of the questions regarding the relationship between cardiorespiratory fitness, hormone replacement, and cardiovascular disease risk factors. However, the study was designed in a way to give us more information about this relationship than was previously available.

Objective Measurement of Cardiorespiratory Fitness

The most important strength of this study was that an objective measure was used to assess cardiorespiratory fitness. Fitness was determined by total time to exhaustion on a graded exercise test (Balke & Ware, 1959). Much of the research on the effects of exercise on cardiovascular disease risk factors have used self reports of exercise which are not always predictive of fitness. Differences have been noted between the benefits of self reported exercise in women, and objectively measured cardiorespiratory fitness (Blair, Kohl, & Barlow, 1993). The advantage of using an objective measure of cardiorespiratory fitness is that there is no self reporting bias. In addition some individuals may lead a highly active lifestyle, but not have a structured exercise program. This type may be mistakenly classified as inactive, when in actuality they are very active.

Variety of Risk Factors Measured Simultaneously

In contrast to previous research, a benefit of this study was that a variety of CVD risk factors were measured simultaneously, including: total cholesterol, HDL cholesterol, total cholesterol/HDL ratio, triglycerides, and fibrinogen. Previous studies on cardiovascular

disease risk factors in postmenopausal women have examined either select blood lipid levels or fibrinogen levels, but not both. An exception to this is the work by Stevenson, Davy, & Seals (1995), in which the effects of hormone replacement on cardiovascular disease risks were evaluated. Their study, however, did not measure cardiorespiratory fitness, hormone replacement was the only predictor variable. In the only two studies which examined the effects of both exercise and hormone replacement on cardiovascular disease risks, blood lipid levels were the only dependent variables, not fibrinogen (Lindheim, et al., 1994; Binder, Birge, & Kohrt, 1996).

Effects of Both Estrogen and Progestin Use on the Outcome Variables

In the current study three groups of postmenopausal women were studied based on their use of hormone replacement. One group used no hormone replacement, a second group used unopposed estrogen, while a third group used both estrogen and progestin. In the experimental study on the effects of exercise and hormone replacement on cardiovascular disease risk factors by Lindheim et al., (1994), subjects were either taking unopposed estrogen, or no hormone replacement. No subjects took a combination of estrogen and progestin. In the research by Binder et al., (1996) subjects either took a combination of estrogen and progestin, or no hormone replacement; no subjects took unopposed estrogen. Thus neither of the previous studies on the combined effect of hormone replacement and exercise examined all three groups: no hormone replacement, unopposed estrogen, and a combination of estrogen and progestin. The current study, therefore, has the advantage of examining the effect of all three possible combinations of

hormone utilization. However the number of subjects in were limited, especially in the group taking both estrogen and progestin.

Limitations

This is a cross sectional study, retrospective in nature. Unlike the experimental studies described earlier it is impossible to infer causation from the results. However, multiple regression allowed a determination of association between cardiorespiratory fitness and the outcome variables, while controlling for possible confounding factors. The likely biological pathway however would be for increased cardiorespiratory fitness to positively affect the outcome variables.

Variability of Hormone Use

The primary limitation of this study was the impossibility of determining the level of hormone replacement, and the length of time on the given hormone replacement. For instance, the most common dosage of estrogen is 0.625 mg/day of Premarin, however, some of the women took a higher dosage such as 1.25 mg/day and some a lower dosage. Also, the route of administration differed. Premarin is taken orally while some women used an estraderm patch and received their estrogen transdermally. These same problems occur with progestin use, in that the amount taken, and the number of days taken per month will vary. In addition, the use of hormones was self reported and many women were unable to recall the dosage that they took.

Dividing the women into individual groups for each possible amount and type of estrogen and progestin would have necessitated a large number of different groups and decrease the number of women in each group. Therefore, the groups were collapsed into

those not taking hormone replacement, those taking unopposed estrogen, and those taking a combination of estrogen and progestin. No distinction was made as to the dosage, route of administration, or number of days the medication was taken per month.

Cardiorespiratory Fitness Assessment

Cardiorespiratory fitness was determined by the individual's total time to exhaustion on a graded exercise test. Direct measurement of maximal VO_2, which is the gold standard, was not performed. Therefore, the current analysis is an estimate of aerobic fitness. This estimate however, has been previously shown to be valid (Foster et al., 1984; Pollock, Wilmore, & Fox, 1978). The protocol used in this analysis has been shown to have a correlation of 0.90 with measured maximal VO_2 in women (Pollock, et al., 1976). It is possible however that some individuals will not push as hard as others and will show an underestimation of their true fitness level. It is unlikely however that this would lead to a systematic bias.

Diet

Diet could have a significant effect of total cholesterol and triglycerides. We were unable to control for diet, due to an unavailability of reliable data. Therefore some of the differences seen, especially in total cholesterol and triglycerides, could be due to a healthier diet in those who were more fit. It is unlikely that diet would have a significant impact on HDL cholesterol or fibrinogen level.

Generalization

The results of this study may not apply to all postmenopausal women. This group was more fit than those in the general population. They are probably more concerned

about health than is the general population as well, since they sought out a preventive medicine physical evaluation. In addition, since the present analysis did not include smokers, this group was more fit than others of similar age from the same data base (46% of women in the highest fitness quintile).

CHAPTER 7: CONCLUSIONS

Implications of Research for the Field of Preventive Care

This research helps clarify the relationship that fitness and hormone replacement have on the cardiovascular disease risk factors of total cholesterol, HDL cholesterol, total cholesterol/HDL cholesterol ratio, triglycerides, and fibrinogen in postmenopausal women. Below is a discussion of these implications.

Implications Regarding Cardiorespiratory Fitness and Cardiovascular Disease

Previous research on women has shown that higher levels of physical fitness are associated with a decrease in cardiovascular and all cause mortality (Blair, et al., 1996). The current research shows some of the mechanisms behind this improved cardiovascular disease risk. In the present analysis fitness was significantly associated with improved levels of total cholesterol ($R^2 = .08$), HDL cholesterol ($R^2 = .04$), total cholesterol/HDL cholesterol ratio ($R^2 = .12$), triglycerides ($R^2 = .09$), and fibrinogen ($R^2 = .06$). Even when controlling for possible confounding factors such as hormone replacement, age, year of testing, and blood glucose levels, cardiorespiratory fitness was still significantly associated with each of the outcome variables. In addition this relationship continued to be significant with the total cholesterol/HDL cholesterol ratio ($R^2 = .02$) and triglycerides ($R^2 = .02$) even after controlling BMI in addition to each of the other control variables. The drop in significance after controlling for BMI is expected since cardiorespiratory fitness is biologically related to body mass, with a decrease in body mass and fat being one of the mechanisms through which exercise and fitness exerts its effect (DiPietro, 1986). The fact that the total cholesterol/HDL cholesterol ratio and triglycerides were

still significantly related to cardiorespiratory fitness, above the effects of BMI and the other control variables indicates an even stronger relationship for these two variables.

Previous research, mostly on men, has typically not shown a significant association between fitness or exercise and total cholesterol, after controlling for confounding factors such as weight (Durstine & Haskell, 1994). The significance between fitness and total cholesterol still held in the present study after controlling for body mass index, hormone replacement, and blood glucose. This would indicate that women may benefit more from a fitness program than men. However, HDL cholesterol has been significantly related to fitness in men even after controlling for weight (Durstine & Haskell, 1994), whereas the significant relationship between fitness and HDL in the present study of postmenopausal women disappeared following control of BMI. More research is needed to determine how men and women respond differently to increased exercise and fitness.

It therefore appears that women and men respond differently to increased levels of cardiorespiratory fitness. Both men and women will benefit from an exercise program, however the specific effects will vary. Postmenopausal women, however, should be encouraged to engage in a regular exercise program since the present study clearly shows that those with higher levels of fitness will improve their cardiovascular disease risk profile regardless of their hormonal status. In addition those women who choose not to take hormone replacement can still significantly reduce their cardiovascular disease risk profile with higher levels of cardiorespiratory fitness.

Implications Regarding Hormone Replacement and Cardiovascular Disease Risk

The use of hormone replacement is very common in postmenopausal women. In the present sample, 61% were taking some form of hormone replacement. The use of unopposed estrogen replacement is associated with an approximate 50% reduction in cardiovascular disease (Bush et al., 1987; Barret-Conner & Bush, 1991). The effect of added progestin is unknown, as most of the studies on the effect of HRT on cardiovascular disease investigated only unopposed estrogen, or they combined those taking progestin with those taking unopposed estrogen. The effect of hormone replacement on various cardiovascular disease risk factors is still debated, but unopposed estrogen replacement is thought to decrease total cholesterol, the total cholesterol/HDL cholesterol ratio, while increasing HDL cholesterol and triglycerides (Lobo, 1991), Unopposed estrogen also decreases fibrinogen levels (Lee, Lowe, Smith, & Tunstall-Pedoe, 1992). Adding progestin to estrogen replacement may negate some of the effect on HDL cholesterol (Hirvonen, Malkonen, & Manninen, 1981; Crona, 1986; PEPI Trial Group, 1995), while also possibly decreasing the triglycerides back to a level typically seen in those not taking hormone replacement (Crook, et al., 1992; Nabulsi et al., 1993).

As can be seen from the present research, postmenopausal women who take either estrogen alone or a combination of estrogen and progestin have a significantly higher HDL cholesterol, and a lower total cholesterol/HDL cholesterol ratio, than women who do not take HRT. No other significant findings of hormone replacement on cardiovascular disease risk factors were found. There was, however, a trend toward increased triglycerides in those taking estrogen alone, while those taking estrogen and

progestin had triglyceride levels similar to those not taking hormone replacement. This trend could be important, since triglycerides have been shown to be a more important risk factor for cardiovascular disease in women than in men (Castelli, 1992; Austin & Hokanson, 1994). In the present study there was also a trend toward decreased total cholesterol and fibrinogen in those women taking a combination of estrogen and progestin. Further research will need to examine the effects of hormone replacement on each of these cardiovascular disease risk factors in order to further clarify the relationship.

Based on these findings women would benefit from taking hormone replacement. The concern regarding a decrease in HDL cholesterol with added progestin was not substantiated in this study. In fact the only effect of added progestin was a non significant trend toward decreasing total cholesterol, triglycerides, and fibrinogen. There were only 59 women (21% of the total) in this study taking a combination of estrogen and progestin. It is possible that if this group were as large as the group taking unopposed estrogen (N=113), or no hormone replacement (N=110), that some of these trends would have been statistically significant.

The addition of progestin to estrogen replacement seems to be a wise decision for those women who have gone through natural menopause. The added progestin does not appear to reduce the cardiovascular benefits of estrogen use, and it may further improve the cardiovascular disease risk profile. Also, the addition of progestin will prevent an increased risk of endometrial cancer (Hulka & Brinton, 1995; Persson, Yuen, Bergkvist, & Schairer, 1996).

Directions for Future Research

Much work still remains to be done in this area. A randomized trial of postmenopausal women into a control group, exercise group, hormone replacement group of both unopposed estrogen and combined estrogen/progestin, and a combination group of exercise and hormone replacement and exercise is needed. Trials similar to this have been done, examining the effect of an exercise program on blood lipid levels (Lindheim et al. 1994; Binder et al., 1996); however, neither study examined both unopposed estrogen and a combination of estrogen and progestin. This, along with differences in the amount and intensity of the exercise treatment, has left many unanswered questions. Following is a list of questions that need to be answered with an appropriate randomized study:

1. Can a group of previously sedentary, postmenopausal women improve their cardiovascular disease risk profile with an exercise program aimed at increasing cardiorespiratory fitness?
2. If so, how much exercise and what intensity of exercise is necessary for these changes to take place?
3. Do these changes occur in all women regardless of hormonal status? (i.e., no hormone replacement, unopposed estrogen replacement, estrogen and progestin replacement)
4. If these changes occur in sedentary women, can women who already exercise further improve their cardiovascular disease risk profile with further increases in exercise and fitness?

Summary

This study has demonstrated that higher levels of cardiorespiratory fitness is associated with a beneficial cardiovascular disease risk profile. This association continues to be significant following control for hormone replacement and other possible confounding factors. In addition, cardiorespiratory fitness has been shown to be a more important indicator of cardiovascular disease risk than is hormone replacement. This due to the fact that cardiorespiratory fitness was significantly associated with each of the measured risk factors, whereas hormone replacement was only significantly associated with HDL cholesterol and the total cholesterol/HDL cholesterol ratio.

Due to this significantly improved cardiovascular disease risk profile that can be achieved with an higher levels of cardiorespiratory fitness, Preventive Care Specialists should strongly encourage a fitness program in postmenopausal women clients, regardless of their hormonal status.

REFERENCES

American College of Sports Medicine. (1995). *ACSM's Guidelines for Exercise Testing and Prescription* (p.18). Baltimore: Williams & Wilkins publishing.

American College of Sports Medicine. (1990). The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness in healthy adults. Position stand. *Medicine and Science in Sports and Exercise, 22,* 265-274.

Anderson, K.M., Castelli, W.P., & Levy, D. (1987). Cholesterol and mortality: 30 years of follow-up from the Framingham study. *Journal of the American Medical Association, 257,* 2176-2180.

Barnes, R.B., Roy, S., & Lobo, R.A. (1985). Comparison of lipid and androgen levels after conjugated estrogen or depo - medroxyprogesterone acetate treatment in postmenopausal women. *Obstetrics and Gynecology, 66,* 216-219.

Barrett-Conner, E., & Bush, T.L. (1991). Estrogen and coronary artery disease in women. *Journal of the American Medical Association, 265,* 1861-1867.

Bass, K.M., Newschaffer, C.J., Klag, M.J., & Bush, T.L. (1993). Plasma lipoprotein levels as predictors of cardiovascular death in women. *Archives of Internal Medicine, 153,* 2209-2216.

Bengtsson, C., Bjorkelund, C., Labidus, L., & Lissner, L. (1993). Association of serum lipid concentrations and obesity with mortality in women: 20 year follow-up of participants in prospective population study in Gothenberg, Sweden. *British Medical Journal, 307,* 1385-1388.

Blair, S.N., Kohl, H.W., & Barlow, C.E. (1993). Physical activity, physical fitness, and all-cause mortality in women: Do women need to be active? *Journal of the American College of Nutrition, 12,* 368-371.

Blair, S.N., Kohl, H.W., Barlow, C.E., & Gibbons, L.W. (1991). Physical fitness and all-cause mortality in hypertensive men. *Annals of Medicine, 23,* 307-312.

Blumenthal, J.A., Emery, C.F., Madden, D.J., Coleman, R.E., Riddle, M.W., Schniebolk, S., Cobb, F.R., Sullivan, M.J., & Higginbotham, M.B. (1991). Effects of exercise training on cardiorespiratory function in men and women older than 60 years of age. *American Journal of Cardiology, 67,* 633-639.

Boyden, T.W., Pamenter, R.W., & Rotkis, T.C. (1987). Effects of exercise training on plasma cholesterol, high density lipoprotein cholesterol, apolipoprotein, A1 and sex steroid levels of early menopausal women. In Eaker, ED. Packard, B. Wenger N.K. Clarkson, T.B. Tyroler, H.A. eds. *Coronary heart disease in women.* New York, NY: Haymarket Doyma, pp.160-163

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

Busby, J., Notelovitz, M., Putney, K., & Grow, T. (1985). Exercise, high density lipoprotein cholesterol and cardiorespiratory function in climacteric women. *South Medical Journal, 78,* 769-773.

Bush, T.L., Barrett-Conner, E., Cowan, L.D., Criqui, M.H., Wallace, R.B., Suchindran, C.M., Tyroler, H.D., & Rifkind, B.M. (1987). Cardiovascular mortality and non-contraceptive estrogen use in women: Results from the Lipid Research Clinics' Program Follow-Up Study. *Circulation, 75,* 1002-1009.

Castelli, W.P. (1992). Epidemiology of triglycerides: A view from Framingham. *American Journal of Cardiology, 70,* 3H-9H.

Cauley, J.A., Laporte, R.E., Kuller, L.H., & Black-Sandler, R. (1982). The epidemiology of high density lipoprotein cholesterol levels in postmenopausal women. *Journal of Gerontology, 37,* 10-15.

Criqui, M.C., Heiss, G., Cohn, R., Cowan, L.D., Suchindran, C.M., Bangdiwala, S., Kritcheusky, S., Jacobs, D.R., O'Grady, H.K., & Davis, C.E. (1993). Plasma triglyceride levels and mortality from coronary heart disease. *New England Journal of Medicine, 328,* 1220-1225.

Crona, N., Enk, L., Mattson, L.A., Samsioe, G., & Silfverstolpe, G. (1986). Progestogens and lipid metabolism. *Maturitas, 8,* 141-158.

Crook, D., Cust, M.P., Gangar, K.F., Worthington, M., Hillard, T.C., Stevenson, J.C., Whitehead, M.B., & Wynn, V. (1992). Comparison of transdermal and oral estrogen/progestin HRT: Effects on serum lipids and lipoproteins. *American Journal of Obstetrics and Gynecology, 151,* 746-750.

Department of Health and Human Services (1991). Healthy People 2000. National Health Promotion and Disease Prevention Objectives. Publication # (PHS) 91-50212.

Duncan, J.J., Gordon, N.F., & Scott, C.B. (1991). Women walking for health and fitness: How much is enough? *Journal of the American Medical Association, 266,* 3295-3299.

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

ECAT Angina Pectoris Study Group. (1993). ECAT angina pectoris study: Baseline associations of haemostatic factors with extent of coronary arteriosclerosis and other coronary risk factors in 3000 patients with angina pectoris undergoing coronary angiography. *European Heart Journal, 14,* 8-17.

Folsom, A.R. (1995). Epidemiology of fibrinogen. *European Heart Journal, 16 (suppl),* 21-24.

Foster, C., Jackson, A.S., Pollock, M.L., Taylor, M.M., Hare, J., Sennett, S.M., Rod, J.L., Sarwar, M., & Schmidt, D.H. (1984). Generalized equations for predicting functional capacity from treadmill performance. *American Heart Journal, 108,* 1229-1234.

Frey, M.A.B., Doerr, B.M., Laubach, L.L., Mann, B.L., & Glueck, C.J. (1982). Exercise does not change high density lipoprotein cholesterol in women after 10 weeks of training. *Metabolism, 31,* 1142-1146.

Gambrell, R.D., & Teran, A. (1991). Changes in lipids and lipoproteins with long term estrogen deficiency and hormone replacement therapy. *American Journal of Obstetrics and Gynecology, 165,* 307-317.

Gibbons, L.W., Blair, S.N., Cooper, K.H., & Smith, M. (1983). Association between coronary heart disease risk factors and physical fitness in healthy adult women. *Circulation, 67,* 977-983.

Goodyear, L.J., Fronsoe, M.S., Van Houten, D.R., Dover, E.V., & Durstine, J.L. (1986). Increased HDL-cholesterol following 8 weeks of progressive endurance training in female runners. *Annuls of Sports Medicine, 3,* 33-38.

Gordon, T., Castelli, W.P., Hjortland, M.C., Kannel, W.B., & Dawber, T.R. (1977). High density lipoprotein as a protective factor against coronary heart disease: the Framingham study. *American Journal of Medicine, 62,* 707-714.

Gordon, D.J., Probstfield, J.L., Garrison R.J., Neaton, J.D., Castelli, W.P., Knoke, J.D., Jacobs, D.R., Bangdiwala, S., & Tyroler, H.A. (1989). High density lipoprotein cholesterol and cardiovascular disease - Four Prospective American Studies. *Circulation, 79,* 8-15.

Haskell, W.L. (1984). The influence of exercise on the concentrations of triglyceride and cholesterol in human plasma. *Exercise and Sport Science Review, 12,* 205-244.

Hardman, A.E., Hudson, A., Jones, P.R.M., & Norgan, N.G. (1989). Brisk walking and plasma high density lipoprotein cholesterol concentration in previously sedentary women. *British Medical Journal, 299,* 1204-1205.

Henderson, B.E., Paganini-Hill, A., & Ross, R.K. (1988). Estrogen replacement therapy and protection from acute myocardial infarction. *American Journal of Obstetrics and Gynecology, 159,* 312-317.

Hill, J.O., Thiel, J., Heller, P.A., Markon, C., Fletcher, G., & DiGirolamo, M. (1989). Differences in effects of aerobic exercise training on blood lipids in men and women. *American Journal of Cardiology, 63,* 254-256.

Hirvonen, E., Malkonen, M., & Manninen, V. (1981). Effects of different progestogens on lipoproteins during postmenopausal replacement therapy. *New England Journal of Medicine, 304,* 560-563.

Holme, I. (1990). An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence. *Circulation, 82,* 1916-1924.

Hulka, B.S., & Brinton, L.A. (1995). Hormones and breast and endometrial cancers: prevention strategies and future research. *Environmental Health Perspectives, 103 suppl,* 185-189.

Jensen, J., Riis, B.J., Strom, V., Nilas, L., & Christianson, C. (1987). Long tern effects of percutaneous estrogens and oral progesterone on serum lipoproteins in postmenopausal women. *American Journal of Obstetrics and Gynecology, 156,* 66-71.

Johnson, C.L., Rifkind, B.M., Sempos, C.T., Carroll, M.D., Bachorik, P.S., Briefel, R.R., Gordon, D.J., Burt, V.L., Brown, C.D., Lippel, K., & Cleeman, J.L. (1993). Declining serum total cholesterol levels among U.S. adults. The National Health and Nutrition Examination Surveys. *Journal of the American Medical Association, 269,* 3002-3008.

Kalin, M.F., & Zumoff, B. (1990). Sex hormones and coronary disease: A review of the clinical studies. *Steroids, 55,* 330-352.

Kannel, W.B., & Gordon, T. (1987). Cardiovascular effects of the menopause. In Mischell, D.R. *Menopause: Physiology and Pharmacology.* Chicago: Year Book Medical Publishers p.92.

Kannel, W.B., Wolf, P.A., Castelli, W.P., & D'Agostino, R.B. (1987). Fibrinogen and risk of cardiovascular disease. The Framingham study. *Journal of the American Medical Association, 258,* 1183-1186.

Kushi, L.H., Fee, R.M., Folsom, A.R., Mink, P.J., Anderson, K.E., & Sellers, T.A. (1997). Physical activity and mortality in postmenopausal women. *Journal of the American Medical Association, 277,* 1287-1292.

Lipid Research Clinics Program (1984). The Lipid Research Clinics Coronary Primary Prevention Trial results II: The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *Journal of the American Medical Association, 251,* 351-374.

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

Meade, T.W. (1995). Fibrinogen in ischaemic heart disease. *European Heart Journal, 16 (suppl A),* 31-35.

Miller, M., Moalemi, A., Seigler, A. Kwiterovich, P., Martos, J., & Pearson, T. (1992). Predictors of cardiovascular mortality in women: A 15 year follow-up study (abstract). *Circulation, 861,* I-674.

Motoyama, M., Sunami, Y., Kinoshita, F., Irie, T., Sasaki, J., Arakawa, K., Kiyonaga, A., Tanaka, H., & Shindo, M. (1995). The effects of long-term low intensity aerobic training and detraining on serum lipid and lipoprotein concentrations in elderly men and women. *European Journal of Applied Physiology, 70,* 126-131.

Omu, A.E., & Al-Qattan, N. (1996). Effect of postmenopausal estrogen replacement therapy on lipoproteins. *International Journal of Gynaecology and Obstetrics, 52,* 155-161.

Paffenbarger, R.S., Hyde, R.T., Wing, A.L., & Hsieh, C. (1986). Physical activity, all-cause mortality, and longevity of college alumni. *New England Journal of Medicine, 314,* 605-613.

Pate, R.R., Pratt, M., Blair, S.N., Haskell, W.L., Macera, C.A., Bouchard, C., Buchner, D., Ettinger, W., Heath, G.W., King, A.C., Kriska, A., Leon, A.S., Marcus, B.H., Morris, J., Paffenbarger, R.S. Patrick, K., Pollock, M.L., Rippe, J.M., Sallis, J., & Wilmore, J.H. (1995). Physical activity and public health: A recommendation from the Centers for Disease Control and Prevention and the American College of Sports Medicine. *Journal of the American Medical Association, 273,* 402-407.

PEPI Trial Group (1995). Effects of estrogen or estrogen/progestin regimens on heart disease risk factors in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *Journal of the American Medical Association, 273,* 199-208.

Persson, I., Yuen, J., Bergkvist, L., & Schairer, C. (1996). Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy - long term follow-up of a swedish cohort. *International Journal of Cancer, 67,* 327-332.

Piani, A., & Schoenborn, C. (1993). Health promotion and disease prevention: Unites States, 1990. *National Center for Health Statistics. Vital Health Stat 10.*

Pollock, M.L., Wilmore, J.H., & Fox, S.M., (1978). Health and fitness through physical activity. New York: Macmillan.

Powell, K.E., Thompson, P.D., Caspersen, C.J., & Kendrick, J.S. (1987). Physical activity and the incidence of coronary heart disease. *Annual Reviews in Public Health, 8,* 253-287.

Razay, G., Heaton, K.W., & Bolton, C.H. (1992). Coronary heart disease risk factors in relation to the menopause. *Quarterly Medical Journal, 85,* 889-896.

Rotkis, T.C., Boyden, T.W., Stanforth, P.R., Pamenter, R.W., & Wilmore, J.H. (1984). Increased high-density lipoprotein cholesterol and lean weight in endurance - trained women runners. *Journal of Cardiac Rehabilitation, 4,* 62-66.

Samsioe, G. (1994). Cardioprotection by estrogens: Mechanisms of action-the lipids. *International Journal of Fertility, 39,* 43-49.

Seals, D.R., Hagberg, J.M., Hurley, B.F., Ehsani, A.A., & Holloszy, J.O. (1984). Effects of endurance training on glucose tolerance and plasma lipid levels in older men and women. *Journal of the American Medical Association, 252,* 645-649.

Sempos, C.T., Cleeman, J.I., Carrol, M.D., Johnson, C.L., Bachorik, P.S., Gordon, D.J., Burt, V.L., Briefel, R.R., Brown, C.D., Lippel, K., & Rifkind, B.M. (1993). Prevalence of high blood cholesterol among U.S. adults. *Journal of the American Medical Association, 269,* 3009-3014.

Shephard, R.J., Youldon, P.E., Cox, M., & West, C. (1980). Effects of a 6-month industrial fitness programme on serum lipid concentrations. *Atherosclerosis, 35,* 277-286.

Stampfer, M.J., & Colditz, G.A. (1991). Estrogen replacement therapy and coronary heart disease: A quantitative assessment of the epidemiologic evidence. *Preventive Medicine, 20,* 47-63.

Stampfer, M.J., Sacks, F.M., Salvini, S., Willett, W.C., & Hennekens, C.H. (1991). A prospective study of cholesterol, apolipoproteins, and the risk of myocardial infarction. *The New England Journal of Medicine, 325,* 373-381.

Stampfer, M.J., Willett, W.C., Colditz, G.A., Rosner, B., Speizer, F.E., & Hennekens, C.H. (1985). A prospective study of postmenopausal estrogen therapy and coronary heart disease. *New England Journal of Medicine, 313,* 1044-1049.

Surgeon General's report (1996). Physical Activity and Health.

United States Department of Commerce (1995). Statistical Abstract of the United States 1995. pp. 92.

Warner, J.G., Brubaker, P.H., Zhu, Y., Morgan, T.M., Ribisl, P.M., Miller, H.S., & Herrington, D.M. (1995). Long-term (5 year) changes in HDL cholesterol in cardiac rehabilitation patients. *Circulation, 92,* 773-777.

Whitehead, M.I., Hillard, T.C., & Crook, D. (1990). The role and use of progestogens. *Obstetrics - Gynecology, 75,* suppl:59-76.

Wilson, P.W.F., Garrison, R.J., & Castelli, W.P. (1985). Post menopausal estrogen use, cigarette smoking, and cardiovascular morbidity in women over 50: The Framingham Heart Study. *New England Journal of Medicine, 313,* 1038-1043.

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