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Relationship between the Percentage of Predicted Cardiorespiratory Fitness and Cardiovascular Disease Risk Factors in Pre-menopausal Women: A Monet Study

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RELATIONSHIP BETWEEN THE PERCENTAGE OF PREDICTED CARDIORESPIRATORY FITNESS AND CARDIOVASCULAR DISEASE RISK FACTORS IN PRE-MENOPAUSAL WOMEN: A MONET STUDY

By
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THESIS

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ABSTRACT

OBJECTIVE: To determine the relationships between the percentage predicted cardiorespiratory fitness (%CRF) and the anthropometric and metabolic cardiovascular disease risk factors in asymptomatic pre-menopausal women. METHODS: Data are baseline values obtained in 97 pre-menopausal women (age: 49.9±1.9yrs; BMI: 23.2±2.2kg/m^2) participating in a longitudinal study. Outcome measures: VO_2 peak, body mass index (BMI), body composition [%fat, fat mass (FM), fat-free mass (FFM)], waist circumference (WC), abdominal subcutaneous adipose tissue (ScAT), visceral AT (VAT), resting blood pressure, fasting lipids, glucose and insulin levels. RESULTS: %CRF was significantly associated with BMI, FM, %fat, WC, ScAT, VAT, triglycerides, triglycerides/HDL-C, total cholesterol, total cholesterol/HDL-C and fasting insulin levels ($-0.59>r<0.31$; $0.01>P<0.05$). The stepwise multiple regression analysis showed that %CRF was only independently correlated with plasma triglyceride levels. CONCLUSION: The results suggest that %CRF was not a major predictor of anthropometric and metabolic variables associated with an increased risk of cardiovascular disease in women. Finally, the use of the %CRF over VO_2 peak needs further studies.

Keywords: cardiorespiratory fitness, cardiovascular disease, body composition, metabolic profile, pre-menopausal women

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LIST OF ABBREVIATIONS

ACE	American College of Endocrinology
APO-B	Apolipoprotein B
AT	Adipose Tissue
BMI	Body Mass Index
BP	Blood Pressure
CHD	Coronary Heart Disease
CRF	Cardiorespiratory Fitness
CT	Computed Tomography
CVD	Cardiovascular Disease
DEXA	Dual-Energy X-ray Absorptiometry
EGIR	European Group for the Study of Insulin Resistance
FFA	Free Fatty Acid
FFM	Fat Free Mass
FM	Fat Mass
HDL-C	High-Density-Lipoproteins Cholesterol
HOMA-IR	Insulin Resistance Homeostasis Model Assessment
HR	Hazard Ratio
HR max	Heart Rate max
HHR	Heart Rate Reserve
LDL-C	Low-Density-Lipoproteins Cholesterol
LPL	Lipoprotein Lipase

NCEP	National Cholesterol Education Program
OGTT	Oral Glucose Tolerance Test
ScAT	Subcutaneous Adipose Tissue
TC	Total Cholesterol
TG	Triglycerides
VAT	Visceral Adipose Tissue
VO_2 peak	Peak oxygen consumption in $mlO_2 \cdot kg^{-1} \cdot min^{-1}$
WC	Waist Circumference
WHO	World Health Organisation
WHR	Waist Hip ratio
% CRF	% Predicted Cardiorespiratory Fitness

CHAPTER 1

A. INTRODUCTION

It is well known that cardiovascular disease (CVD) is the first cause of mortality in many developed countries (1). Cardiovascular disease is responsible for 30 percent of deaths worldwide each year (2). When it comes to women, it is the leading cause of death. Half a million women die of CVD each year and most of them are asymptomatic (3). What is really disturbing is the fact that 50 percent of women are not aware that CVD is the leading cause of death (4). It was reported that women who are aware were more likely to attribute their CVD to external factors, such as, family history than to major modifiable risk factors such as obesity (5). Many CVD risk factors have been identified and well established: obesity, dyslipidemia, physical inactivity, diabetes, hypertension, smoking and psychosocial factors (6). Depending on the nature and/or the number of factors, the individual risk of CVD may vary from low to high. Pre-menopausal women have a lower risk of cardiovascular disease compared to post-menopausal women (7). It is thus possible that the menopause transition per se increases risk of CVD in women.

The prevalence of obesity has increased, and is still increasing dramatically in developed countries (9) and it is recognized as one of the most important risk factor to morbidity and mortality (10). It's associated with many chronic diseases including CVD, diabetes, cancer and depression (9, 11). Moreover, abdominal obesity, especially visceral obesity, is associated with an increasing risk of metabolic syndrome, CVD and type 2 diabetes and can lead to premature death (12, 13).

Dyslipidemia is "the presence of an abnormal lipid/lipoprotein profile and can be classified as: predominant hypertriglyceridemia, hypercholesterolemia or mixed pattern with elevation of both total cholesterol (TC) and triglycerides (TG)" (14). High plasma concentration of low-density-lipoproteins cholesterol (LDL-C) and low plasma level of high-density-lipoproteins cholesterol (HDL-C) are strongly associated with a higher risk of cardiovascular disease (8).

The metabolic syndrome, which is characterized by: abdominal obesity, dyslipidemia, high blood pressure (BP), glucose intolerance/insulin resistance (15) is common and affects 40 to 50 million people in the United States (15) and is also associated with an increased risk of CVD and type 2 diabetes.

Regular physical activity has a positive influence on the risk of cardiovascular disease (16). It is defined as a form of leisure and non-leisure body movement produced by the skeletal muscles and was demonstrated to be inversely proportional with the risk of CVD (17, 18). On the other hand, exercise is defined as a form of leisure-time physical activity that is planned, structured and repetitive (17). The practice of regular physical activity or exercise, either light or moderate, is associated with a decrease of the prevalence of CVD and the rate of CVD death (18). Notably, the more physical activity is practiced, lower is the cardiovascular disease risk compared to sedentary individuals (16, 18).

Cardiorespiratory fitness (CRF) has been demonstrated to be an independent predictor of the risk of death and cardiac events among asymptomatic women (19). Low aerobic fitness is an independent risk factor for CVD and is also associated with an increased risk of metabolic syndrome (20, 21). In addition, fit individuals have lower

rates of metabolic health disturbances, such as the metabolic syndrome, than those who are unfit (22).

It is important to point out that in clinical practice, there is a need for effective CVD risk stratification for women, especially asymptomatic women. Risk assessment tools were therefore developed to predict or stratify individuals at risk for CVD. Just to name a few, the metabolic syndrome, the Framingham score and the percentage predicted cardiorespiratory fitness (% CRF) are tools used. Of the three, only the % CRF seems to be a good predictor to identify asymptomatic women at risk for cardiovascular disease (19). However, the author's failed to adjust the % CRF for other independent anthropometric and metabolic CVD risk factors in their study. Therefore, % CRF may only be a good proxy of the already established CVD risk factors (ex. visceral adipose tissue, TG, insulin, etc). Despite little supportive research, it is important to document if there are relationships between anthropometric, metabolic CVD risk factors and % CRF in a cohort of well-phenotyped pre-menopausal women.

The content of this thesis is comprised of several chapters: the first is the literature review which includes: 1. cardiovascular disease risk factors; 2. physical activity and CVD risk factors; 3. cardiorespiratory fitness and CVD risk factors; 4. the cardiovascular disease risk assessment tools; 5. the menopausal status. Second chapter presents the purpose and hypothesis of the study. Fourth chapter is reserved for the original article, presenting altogether the method, results and general discussion. Finally, the fifth chapter presents the conclusions and perspectives of this study.

B. LITERATURE REVIEW

1. Cardiovascular Disease Risk Factors

1.1.Obesity

Obesity is defined as an excess weight, especially an excess body fat (23). Obesity is associated with an increased risk of insulin resistance, type 2 diabetes and CVD (23, 11). Obesity is among the top health risk factor for the American and Canadian population; men, women and children of all age and ethnic group (24, 25). The prevalence of obesity has increased in Canada over recent years, there was approximately a 14% increase from 1972 to 2005 among Canadian adults (Figure 1) (25). It can be caused by many factors such as genetic, unhealthy nutrition and physical inactivity (23). Obesity can be defined as body mass index (BMI), higher than 30 kg/m^2, where weight (kg) is divided by height (m^2), or categorised by having a % fat of $\geq$ 35% in women (26, 27). However, a study by Romero-Coral *et al.* (27) have shown that BMI can miss more than half of individuals with a true excess in body fat. They found that BMI was strongly correlated with % fat, but failed to discriminate between lean mass and fat mass in cross-sectional study of 95 patients with coronary heart disease (CHD). Studies have also shown that % fat is a predictor of cardiovascular risk factors (28, 29). As reported in a previous study, % fat was found to be a strong independent factor for elevated systolic and diastolic blood pressure, TG, LDL-C, and LDL-C/HDL-C ratio and a reduced HDL-C, altogether increases the risk of CVD (29). Furthermore, in a cohort of 115,886 U.S. women, 605 were identified with coronary events, 306 with nonfatal myocardial infarctions, 83 deaths due to CHD and 216 cases of angina pectoris. Obesity was found to be positively associated with these events in this population of women (30).

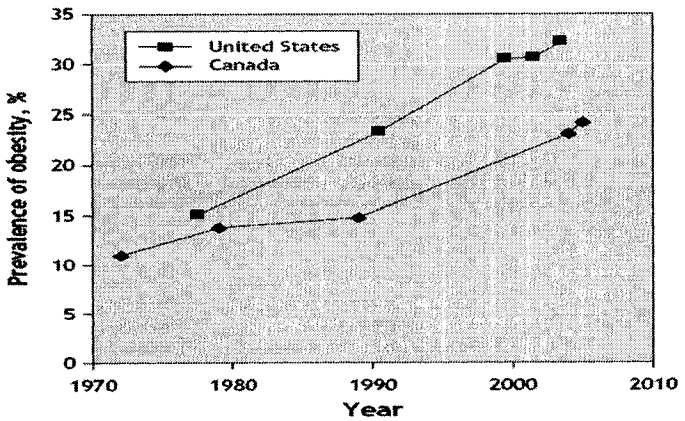

Figure 2. The prevalence of Obesity in Canada and the United States.
Source: With permission (Appendix E), CMAJ, 2006 (28) Canadian clinical practice guidelines on the management and prevention of obesity in adults and children.

1.2.Abdominal Obesity

An increase in abdominal obesity, especially visceral fat area (>130 cm^2), is accompanied by an exponential elevation of TG, reduced HDL-C, high BP, elevated plasma glucose and insulin resistance (31). Therefore, visceral obesity plays a major role in the development of the metabolic syndrome and cardiovascular disease (Figure 2) (12, 32, 33).

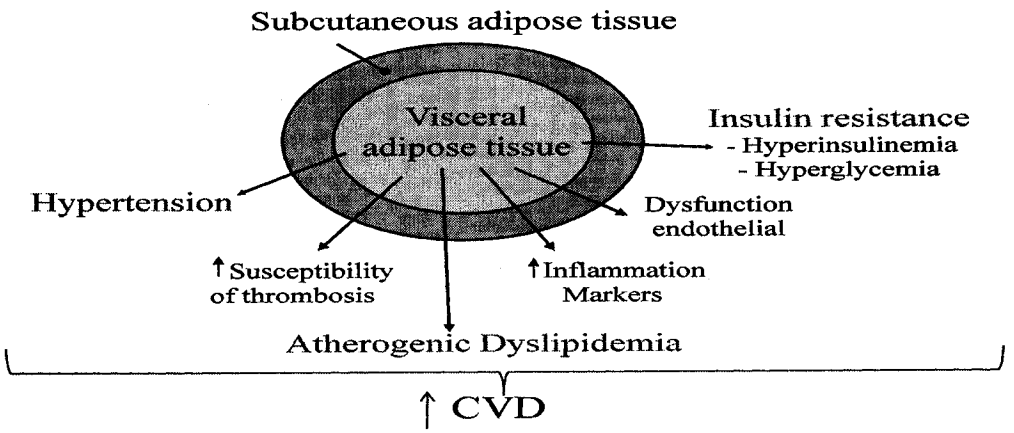

Figure 3. Potential mechanism of increased visceral adipose tissue leading to cardiovascular disease. Source: adapted from Despres, J.P. *et al.* (34)

In women, the amount of visceral adipose tissue (VAT) stored in the intra-abdominal cavity is an independent risk factor for myocardial infarction (35). Post-menopausal women are more prone to central obesity than pre-menopausal and perimenopausal women. It is suggested that perimenopause compared with early post-menopause status, is associated with significant differences in adipose tissue metabolism in both abdominal and gluteal fat depots. The lower basal lipolysis in gluteal adipose cells and the higher lipoprotein lipase (LPL) activity in both gluteal and abdominal adipose cells in post-menopausal women may predispose them to gain more body fat compared to perimenopausal women (36). Furthermore, after a 12 week weight reduction program including 21 pre-menopausal and 19 post-menopausal obese women, it was found that the post-menopausal women lost less VAT compared to the pre-menopausal group (37). Possible reasons for this fact are: VAT is or could be more sensitive to changes during weight reduction in pre-menopausal women and to sex hormone which are deficient in post-menopausal women; another reason could simply be that post-menopausal women had more VAT to start with (37).

The increase in abdominal fat is another phenotype that explains the higher risk of CVD and metabolic disease in post-menopause women (38, 39). A cross-sectional study of 2892 pre- and post-menopausal women (aged 20 to 78 years; BMI $\geq$ 25) divided women into quartiles based on their waist to hip ratio (WHR). The results showed that in overweight and obese women, chances of having cardiovascular risk factors (low HDL-C, high TG, high TC/HDL-C and high fasting blood sugar) increased with WHR $\geq$ 0.78 in pre-menopausal and with a WHR $\geq$ 0.84 in post-menopausal women (40). Furthermore, it has been proven that obese post-menopausal women have significantly

higher waist circumference (WC), WHR and visceral fat volume compared to obese pre-menopausal women matched for body mass index (41).

1.3.Dyslipidemia

Dyslipidemia is a disorder where plasma level of: TG $\geq$ 1.7 mmol/l, LDL-C $\geq$ 3.5 mmo/l, TC $\geq$ 5.0 mmol/l and HDL-C $\leq$ 1.3 mmol/l for women (15). Dyslipidemia is considered to be a primary risk factor for CHD (42). It was reported that both TG and HDL-C plasma levels are considered strong predictors of CVD among women (43). Women in the highest quintile of triglycerides had a 2.45-fold greater risk of CVD mortality than women in the lowest quintile, and the risk was increased to 3.81-fold, with low HDL-C plasma level (44). In women, it's known that a low level of circulating oestrogens is associated with high LDL-C and/or low HDL-C plasma levels (45). It was also found that plasma levels of TC, after menses have ceased, are increased according to studies (46, 47, 48). In a study comparing pre- and post-menopausal women of same age, BMI and WHR, showed that the post-menopausal women had a 10%, 14% and 8.2% increase in TC, LDL-C and apolipoprotein B respectively (49). In that same study, they did not find any difference in blood glucose, insulin, TG, HDL-C, apolipoprotein A1, and systolic and diastolic blood pressure. Therefore, their results concluded that TC, LDL-C and apolipoprotein B are the primary CVD risk factors affected by menopause.

1.4.Metabolic Syndrome

The metabolic syndrome represents a major risk factor for the development of CVD (13). The metabolic syndrome was characterized by Eskil Kylin, in 1923, by the

cluster of phenotype such as hypertension, hyperglycemia, obesity, and hyperuricemia in individuals. Since then, many definitions have been proposed, but only four are being used nowadays (13), the National Cholesterol Education Program (NCEP), the World Health Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR) and the American College of Endocrinology (ACE) (Table 1) (50). All four include measurement of BP, TG, HDL-C and fasting glucose (50).

Table 1. Metabolic Syndrome definitions.

	NCEP[1]	WHO[2]	EGIR[3]	ACE[4]
Required	---	Insulin in top 25%; glucose ≥ 6.1 mmol/L; 2 hour glucose ≥7.8 mmol/L	Insulin in top 25%	High risk: BMI > 25 kg/m^2 or waist ≥ 102 cm (men) or ≥ 88 cm (women)
No. of abnormalities	**≥ 3 of:**	**And ≥ 2 of:**	**And ≥ 2 of:**	**And ≥ 2 of:**
Glucose	≥ 6.1 mmol/L		≥ 6.1 mmol/L	≥ 6.1 mmol/L; 2 hour glucose ≥ 7.8 mmol/L
HDL-C	< 1.0 mmol/L (men); < 1.3 mmol/L (women)	< 0.9 mmol/L (men); < 1.0 mmol/L (women)	< 1.0 mmol/L	< 1.0 mmol/L (men); < 1.3 mmol/L (women)
		or	or	
Triglycerides	≥ 1.7 mmol/L	≥ 1.7 mmol/L	≥ 2.0 mmol/L	≥ 1.7 mmol/L
Obesity	Waist ≥ 102 cm (men); ≥ 88 cm (women)	Waist/hip ratio > 0.9 (men) or > 0.85 (women); BMI ≥ 30 kg/m^2	Waist ≥ 94 cm (men); ≥ 80 cm (women)	
Hypertension	≥ 130/85 mm Hg	≥ 140/90 mm Hg	≥ 140/90 mm Hg	≥ 130/85 mm Hg

Source: adapted from Dekker, J.M. *et al.* (50).
[1]National Cholesterol Education Program; [2]World Health Organization;
[3]European Group for the Study of Insulin Resistance; [4]American College of Endocrinology

The one which is the most widely used is the NCEP definition who define the metabolic syndrome as the presence in an individual of at least three of the five following parameters: waist circumference for men >102 cm, for women >88cm; fasting glucose ≥6.1 mmol/L; low HDL-C <1.0 mmol/L for men, <1.3 mmol/L for women; TG ≥1.7

mmol/L; and/or hypertension ≥130/85mmHg (51). A study showed that both men and women with metabolic syndrome are associated with a 2-fold increased risk incidence of cardiovascular disease (50).

2. Physical Activity

2.1.Obesity

Low levels of physical activity have been shown to be associated with a higher level of body weight (52) consequently higher risk of CVD. Hu *et al.* (53) demonstrated that the risk of mortality of CVD decreases in obese active women, and diminishes even more in non-obese active women compared to obese and non-obese women who are physically inactive. A strong relation has been established between BMI and physical activity, and exercise has been shown to have a strong independent inverse effect on BMI (53, 54, 55). Lamonte *et al.* (56), showed that BMI and WC decreases depending on the exercise intensity and volume from low (< 276 MET-minutes/day) to moderate (276-480 MET-min/day) to high (> 480 MET-min/day). More evidence was shown by Blair & Brodney (18): regular physical activity attenuates many health risks associated with overweight or obesity; physical activity appears to not only attenuate the health risks of being overweight or developing obesity, but overweight and obese individuals who achieve adequate level of physical activity actually have lower morbidity and mortality than normal weight individuals who are sedentary; physical inactivity is also a very important mortality predictors. A study by Sternfeld *et al.* (57) has noted that women in the late peri- and post-menopausal had higher % body fat, WC and lower lean mass compared to pre-menopausal women. Women who engaged in higher level of physical

activity showed significantly lower % body fat and WC. It was suggested in this study that regular physical activity may help reduce the risk of weight gain and prevent the negative changes in body composition and fat distribution observed during the menopausal transition.

2.2.Abdominal Obesity

It is also clear that physically active people have reduced abdominal obesity compared to sedentary people (58). Although visceral obesity accumulation during menopause increases the risk of metabolic abnormalities and CVD, physical activity seems to counteract it (59). It was determined that physical activity was negatively and significantly correlated with VAT accumulation (60). Many studies have confirmed that physical activity attenuates the accumulation of visceral adipose tissue and the associated CVD risk in women (61, 62, 63).

2.3.Dyslipidemia

Regular physical activity is associated with a lower risk of CVD partly because it improves the lipoprotein profile (64). Improvement in lipoprotein profile was seen (↓ TG, TC, LDL-C and ↑ HDL-C) among participants who jogged 17 to 18 miles per week, than those who exercised at a lower volume (64). It is known that during menopause the level of estrogens is reduced and it is associated with a higher risk of dyslipidemia (65). However, it was reported that in post-menopausal women who participated in regular physical activities had a lower TG plasma concentration, TC/HDL ratio and higher high-density-lipoproteins cholesterol (60).

2.4.Metabolic Syndrome

Physical activity plays a key role in the management of the metabolic syndrome (65). For the most part, regular physical activity prevents: obesity, insulin resistance, glucose intolerance, type 2 diabetes, dyslipidemia and elevated BP, altogether preventing the development of the metabolic syndrome in individuals (66). In obese pre-menopausal women with the metabolic syndrome who underwent a 3 month lifestyle intervention, which consisted of physical activity and a psychological framework on healthy eating, body weight management and general well-being, showed an improvement in cardiorespiratory fitness, blood pressure, HDL-C and a modest reduction in body mass (67). Furthermore, physical activity associated with a balanced diet, and hormone replacement therapy in post-menopausal women has been shown to decrease the risk of CVD due to an improvement of the metabolic syndrome features (68).

2.5. Cardiovascular disease

Regular physical activity is known as one of the best strategy for cardiovascular disease prevention (69), favour a healthy body composition (70) and blood lipids (71) in women. Many studies have found that light-to-moderate (16) or high-intensity (72) exercises are associated with a lower CVD rate in women. Overall, moderately active and highly active individuals have lower risk of stroke or mortality by 20% and 27% respectively than the low-active individuals (73). It was noted that women who are active during the adulthood years are more likely to be active when older; therefore the risk of CVD is predicted to be lower (74). Another study found that the relative risks of death from any cause and CVD among participants with different risk factors (hypertension,

chronic obstructive pulmonary disease, diabetes, smoking, BMI $\geq$ 30, and high TC $\geq$ 5.70 mmol/L) are lower for those who achieved exercise more than 5 METs (metabolic equivalents) than those who achieved less than 5 METs per day (75).

3. Cardiorespiratory Fitness

3.1.Obesity

Low cardiorespiratory fitness is associated with an increase risk of obesity (62). Compared to lean and fit women, the risk of CVD mortality increases from obese fit women, lean unfit women to obese unfit women (76). Another study has reported that overweight or obese women with a high level of CRF have higher insulin sensitivity, than sedentary obese individuals with low CRF (77). Further results confirm that CRF is significantly decreased in obese women compared to lean women, and VO_2 per kilogram fat-free mass for both groups is negatively related to BMI (r = -0.37) and percentage fat mass (r = -0.40) (78). In 44 obese, sedentary, post-menopausal women, an increase in physical activity and CRF showed a reduction in body weight (26.5%), fat mass (27.4%) and % body fat (22.4%) after a 6 months lifestyle change intervention (79).

3.2.Abdominal Obesity

In a study performed by Ross, R. *et al.* (80) in abdominally obese pre-menopausal women reported that VAT alone is strongly correlated with insulin resistance independent of abdominal subcutaneous AT, muscle AT and CRF. A decrease in CRF has been shown to be associated with an increase in VAT witch leads to a cluster of metabolic disturbance and CVD (Figure 4) in individuals (81). In Japanese women, it was demonstrated that

there were significant inverse correlation between oxygen uptake at ventilatory threshold and visceral fat area (r = - 0.40) (82). High CRF ≥ 43.0 $mlO_2 \cdot kg^{-1}min^{-1}$ (men) and ≥ 33.0 $mlO_2 \cdot kg^{-1}min^{-1}$ (women) was associated with a significant reduction in total and abdominal obesity compared to low CRF < 38.0 $mlO_2 \cdot kg^{-1}min^{-1}$ (men) and < 29.0 $mlO_2 \cdot kg^{-1}min^{-1}$ (women) for a given BMI (83). Lynch *et al.* (84) performed a study that aimed to determine whether the loss of VAT is related to improvements in maximal O_2 uptake, during a weight loss program and walking intervention in post-menopausal women. The program resulted in a significant reduction in body weight, total fat mass, VAT, and subcutaneous AT area with no change in lean body mass. The reduction in VAT was negatively correlated with the improvement of VO_2 max (r = -0.47), and 30% of the inter-individual change in VAT was explained by a change in VO_2 max and fat mass. Women who increased their VO_2 max by 10% present a 20% reduction in VAT compared to those who did not increase their VO_2 max.

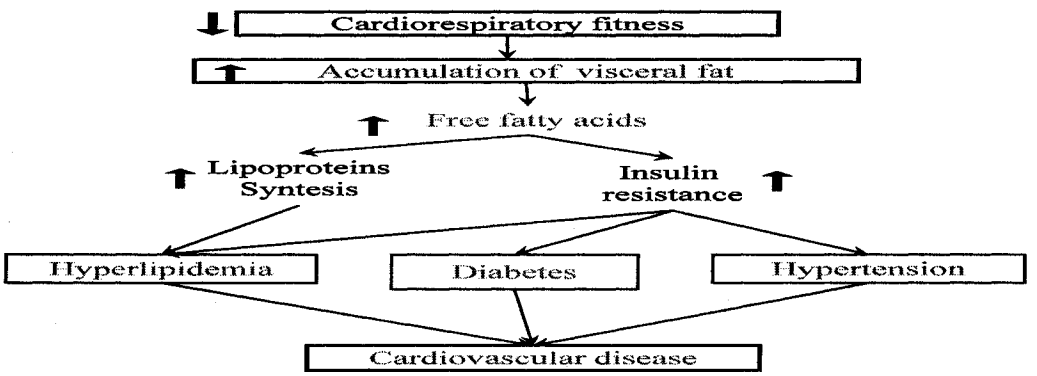

Figure 4. Potential mechanism of certain diseases related to a low cardiorespiratory fitness and visceral obesity. Source: adapted from Matsuzawa, Y. *et al.* (81).

3.3.Dyslipidemia

Regular physical activity and improvement in cardiorespiratory fitness has been shown to increase HDL-C and decrease TG plasma levels (85). In women, inverse associations were found for TG and TC/HDL-C ratio, and a positive association for HDL-C with CRF (86). Even in post-menopausal women, CRF was shown to improve plasma lipid level after a 26 months intervention (87). Higher level of CRF is significantly associated with TC ($r = -0.32$), TC/HDL-C ($r = -0.35$), TG ($r = -0.32$), and HDL-C ($r = 0.18$) (88). In that study they concluded that CRF is an important independent determinant of blood lipid in post-menopausal women.

3.4.Metabolic Syndrome

Cardiorespiratory fitness has been shown by many researchers to be associated with a reduced body weight, BP, TC, TG, LDL-C, an increased HDL-C (79), and insulin sensitivity (77). The prevalence of metabolic syndrome was found to be 6 times higher in less fit versus fit men and 4 times higher in less fit versus most fit women. Also fitness index was negatively associated with most of the components of the metabolic syndrome, except for HDL-C which was positively correlated (89). LaMonte and colleagues (90, 91) conducted in two separate studies at evaluating 1) the relationship between CRF and the prevalence of metabolic syndrome in men and women, and 2) the relationship between CRF, C-reactive protein and metabolic syndrome in women. In both studies, CRF was found to be a strong and independent predictor of the presence of the metabolic syndrome.

3.5.Cardiovascular disease

It is important to specify that cardiorespiratory fitness, as defined by maximal aerobic capacity (VO_2 max or VO_2 peak) measurements, is another important risk factor of CVD. A decline in CRF is associated with an increase risk of CVD, particularly CHD (92) partly due to an increase in obesity, hypertension, and diabetes (93). In a study performed by Dvorak *et al.* (94) it was found that high levels of CRF (>27.7 $ml \cdot kg^{-1}min^{-1}$ for men and >21.7 $ml \cdot kg^{-1}min^{-1}$ for women) have greater cardioprotective effects than high levels of physical activity in 53 men (68±6.9 yrs) and 63 women (67±6.7 yrs). In healthy women, menopause is associated with cardiopulmonary abnormalities caused by oestrogen deficiency and a reduced level of nitric oxide. This accounts for an impairment of endothelium-dependent vasodilation, preventing O_2 flow from matching the O_2 requirement during exercise (95). Lynch *et al.* (96) demonstrated that post-menopausal women have lower (-17%) VO_2 max compared to perimenopausal and pre-menopausal women of similar age and adiposity, suggesting a higher risk of CVD. The following table shows the cardiorespiratory fitness levels for females.

Table 2. Reference ranges for low, moderate and high cardiorespiratory fitness levels for female adults between the age of 40-49 years.

	Females
CRF	**40 – 49**
Low	≤ 26.54
Moderate	26.55 – 32.30
High	≥ 32.31

Source: adapted from Duncan, G.E *et al.* (97).
CRF: cardiorespiratory fitness.

The recommended guidelines for exercise to maintain CRF and body composition according to the American College of Sport Medicine for healthy adults are as followed (98):

1. Frequency: 3-5 days/week, preferably everyday.
2. Intensity: 55/65%-90% of maximum heart rate (HR max), or 40/50%-85% of maximum oxygen uptake reserve (VO_2 R) or HR max reserve (HRR). For individuals who are unfit, lower intensity values, 40-49% of VO_2 R or HRR and 55-64% of HR max, are more applicable.
3. Duration: 20-60 min of continuous of intermittent (minimum of 10-min bouts accumulated throughout the day) aerobic capacity.

Mode: any activity that uses large muscle groups, e.g., walking-hiking, running-jogging, cycling-bicycling, cross-country skiing, aerobic dance/group exercise, rope skipping, rowing, stair climbing, swimming, skating and various endurance activities.

3.6.Genetic factor

Cardiorespiratory fitness is a measure of functional capacity measured by maximal oxygen consumption (99). There is no doubt that physical activity and nutrition are essential for improving CRF, however these factors alone are not sufficient (100). There is also the genetic factor which plays an important role in CRF, and its contribution can vary between 20 to 50% in individuals (101, 102). Cardiorespiratory fitness phenotypes such as heart size, cardiac and pulmonary functions are also influenced by genetic factors, and heritability can vary from 30% to 70% (101). Therefore an individual with a higher stroke volume, cardiac output, forced expiratory volumes, forced vital capacity and larger heart, can benefit from higher CRF when such phenotypes are inherited. Bouchard *et al.* (103) demonstrated that VO_2 max includes a significant genetic

component and yielded a maximal heritability estimate of 47% in 481 sedentary adult Caucasians from the HERITAGE Family study. Their results also revealed that there was twice as much variance between families than within families in the VO_2 max response to exercise training. In another study, it was revealed that sensitivity of maximal aerobic power to training is largely genotype-dependent explaining approximately 75% of the variance in ten pairs of monozygotic twins who underwent a 20 week endurance training program on a cycle ergometer (104).

4. Cardiovascular Disease Risk Assessment Tools

Predicting a person's cardiovascular risk has become important especially for individuals who are asymptomatic and at high risk of CVD. Using risk assessment tools can help targeting preventive treatment for people who are at high risk for CVD (105). There are many tools available, some can be used by the patient at home and others can be performed by a health professional at a clinic or hospital. The CVD risk assessment tools that will be reported in this paper are: the metabolic syndrome, the Framingham risk score and the nomogram of the percentage of predicted cardiorespiratory fitness.

4.1.Metabolic Syndrome

The metabolic syndrome is defined as a cluster of risk factors, including obesity, hypertension, hyperglycemia, and dyslipidemia (15) and affects on average 15% and 25% of the Canadian and American population (106). It is associated with an increased risk of CVD mortality, and this risk is greater in women than in men (107), the risk increases significantly and progressively with increasing number of metabolic abnormalities (108).

In a prospective study of 5128 men observed for 20 years, researchers has found that the probability of developing CVD increased from 11.9% to 31.2% and to 40.8% in individuals with no abnormalities, 3 abnormalities and 4 or 5 abnormalities respectively (109). In a 15 year follow-up study of 685 Sicilian subjects, where 387 were females, it was shown that the metabolic syndrome was significantly more prevalent in women (31.5%) than in men (12.4%) and was predictive of CVD events regardless of the presence of glucose intolerance or diabetes mellitus (110).

4.2.Framingham Risk Score

Information from The Framingham Heart Study on the World Wide Web (111)

The Framingham score prediction algorithm provides estimates of total CHD risk either: angina pectoris, myocardial infarction over the next 10 years. Separate score sheets are used for men (Appendix A) and women (Appendix B), it is the same procedure but the assigned points and values differ for each factor. The factors used for the risk estimation include age, LDL-C, HDL-C, BP, cigarette smoking, and diabetes. The risk for CHD is estimated by comparing the average 10 year CHD risk to the low risk Framingham participants of same age. Higher values means higher risk for CHD. Individuals with less than 6% risk for coronary events over 10 years are at low risk, those between 6% and 20% are at intermediate risk and > 20% are at high risk (112). In a report by Mieres *et al.* (113) it was revealed that 64% of women between the age of 50 and 79 were at intermediate or high risk with a 10 year risk of > 6%. However the risk for CHD can be reduced if certain measures are taken such as weight loss. In the Framingham cohort, those who lost at least 2.25 kg over 16 years had reduced half their total risk factor score

(114). The following information are limits to the risk prediction score sheets (copied as is from the The Framingham Heart Study).

1. *The risk estimating score sheets are only for persons without known heart disease.*
2. *The Framingham Heart Study risk algorithm encompasses only coronary heart disease, not other heart and vascular diseases.*
3. *The Framingham Heart Study population is almost all Caucasian. The Framingham risk algorithm may not fit other populations quite as well.*
4. *For some of the sex-age groups in Framingham, the numbers of events are quite small. Therefore, the estimates of risk for those groups may lack precision.*
5. *Other organizations are considering how the information from the Framingham risk algorithm, as well as other assessments of risk, might best be incorporated into clinical practice.*
6. *The Framingham risk score estimates the risk of developing CHD within a 10-year time period. This risk score may not adequately reflect the long-term or lifetime CHD risk of young adults, which is: one in two for men and one in three for women.*
7. *The presence of any CHD risk factor requires appropriate attention because a single risk factor may confer a high risk for CHD in the long run, even if the 10-year risk does not appear to be high.*
8. *Since age is a prominent determinant of the CHD risk score, the 10-year hazards of CHD are, on average, high in older persons. This may over-identify candidates for aggressive interventions. Relative risk estimates (risk in comparison with low risk individuals) may be more useful than absolute risk estimates in the elderly.*
9. *The score derived from this algorithm* ***should not*** be used in place of a medical examination.

The Framingham Heart Study (111).

4.3.Nomogram of the Percentage of Predicted Cardiorespiratory Fitness (% CRF)

A nomogram has been developed to predict the risk of mortality using the CRF based on the age of both asymptomatic and symptomatic women (19). A total of 5721 asymptomatic women and 4471 symptomatic women between the age of 34 and 93 underwent a symptom limited maximal stress test. A linear regression equation was established to predict the CRF in metabolic equivalent (MET) based on age in the

asymptomatic women cohort (MET = 14.7 – (0.13 x age)). The authors in this study confirmed that the risk of mortality from cardiac cause in the asymptomatic women cohort with a CRF of less than 85% of the age predicted value was twice (hazard ratio (HR) of 2.44) as much higher than among women whose CRF was at least 85%. The nomogram (see Appendix C) requires only the women's age and the CRF achieved in MET. By drawing a straight line between the age and the CRF, the percentage of predicted CRF for age can be determined. It can also be calculated by using the following equation: %CRF = (MET observed / (14.7 – (0.13 x age))). Any value higher than 100 percent indicates a better performance and a reduced risk of mortality and any value lower than 100 percent indicates some cardiorespiratory functional impairment (19). In a recent study performed by Peterson, *et al.* (115), on 9191 subjects followed for 2.7 years, have shown that a %CRF less than 85% of the predicted CRF was associated with an increased risk of myocardial infarction (HR = 2.36), unstable angina (HR = 2.39), coronary revascularization (HR = 1.75) and all-cause mortality (HR = 2.90) compared with individuals with a capacity higher than 85%. The authors have concluded that a low %CRF was associated with both nonfatal cardiovascular events and mortality.

5. Menopause Status

It is necessary nevertheless to define the different menopausal stages. Menopause is defined as "the permanent cessation of menstruation, resulting from the loss of ovarian follicular activity" (116). Pre-menopause is defined as the period preceding menopause (117). Perimenopause is defined as the period around the onset of menopause that is often marked by various physical symptoms and/or signs such as menstrual irregularity and hot

flashes (118). Post-menopause is the period occurring after menopause but cannot be diagnosed until 12 months of spontaneous amenorrhoea is observed (116).

The incidence of CVD increases sharply after the middle age in women especially after the menopause (49). Such incidence may be related to substantial metabolic and body composition changes that occur from pre-menopause to post-menopause. Menopause is a period that is associated with increased fat mass, abdominal adiposity, lipids and lipoproteins and features of the metabolic syndrome (119, 120, 121, 49). Oestrogen deficiency has been suggested to be the underlying cause of these major modifications which leads to a rapid acceleration in CVD risks in women (121). Moreover, it has been previously shown that CRF decreases in post-menopausal women compared to pre-menopausal women of same age (95, 96). As for the effect of different menstrual phase (follicular, ovulatory and luteal) in women on CRF, many studies have found no significant difference during any phase of the menstrual cycle on CRF (122, 123, 124). A study by Smekal, *et al.* (125) tested 19 eumenorrheic physically active women (mean age: 26.6 years) on a cycle ergometer until voluntary exhaustion during two different phases of the menstrual cycle (follicular phase and luteal phase). When they compared power output, VO_2 max, lactate concentration, heart rate, they found no significant differences between the follicular and luteal phase at rest or at maximal load. Another group tested 30 sedentary high altitude (>3000 m) native women between the age of 23 and 35 years on a cycle ergometer and also found no effect on VO_2 max (122). Overall, it does not appear as if CRF are significantly different during any phase of the menstrual cycle.

C. SUMMARY

Throughout this section we have presented many modifiable factors that increase the risk of CVD. Obesity, visceral obesity, an elevated plasma TG, TC, LDL-C, a reduction in HDL-C and the metabolic syndrome. These risk factors are prone to increase as women get past menopause; women after that stage are therefore at a higher risk of developing CVD compared to pre-menopausal women. Physical activity and CRF were proven to be positive health factors and associated with a reduction in many risk factors, the prevalence of CVD and mortality. Among the risk assessment tools presented, the nomogram of the predicted CRF was recently developed to predict the risk of mortality due to cardiac causes in asymptomatic women using the % of predicted CRF for age. Moreover, CRF has been demonstrated to be an independent predictor of the risk of death and cardiac events among asymptomatic women.

The present objectives of the study are to use the nomogram to assess the CVD risk of asymptomatic pre-menopausal women. Also, to investigate the relationships between the % predicted CRF and the CVD risk factors and finally to determine if the percentage of predicted cardiorespiratory fitness for a given age is an independent determinant of the inter-individual variation observed in anthropometric and metabolic cardiovascular disease risk factors.

For the purpose of this study the risk factors that will be studied, will be the ones that account for the most of the risk of CVD worldwide in both sexes mentioned by Yusuf *et al.* (126). Of those factors, abnormal lipids (TC, TG, LDL-C, HDL-C), hypertension, obesity (BMI, % fat), abdominal obesity (VAT, ScAT) will be looked at. Also, waist circumference and plasma glucose will be studied since they are part of the

metabolic syndrome (50). Finally, plasma insulin, insulin resistance and/or insulin sensitivity will also be studied since they have been strongly associated with the risk of cardiovascular disease (77).

CHAPTER 2

A. SPECIFIC PROBLEM

As mentioned previously, there is a need for effective CVD risk stratification in clinical practice for women. Out of the three tools described in the literature review (metabolic syndrome, Framingham score and %CRF), the % CRF seems to be a good predictor to identify women at risk for cardiovascular disease, especially asymptomatic women without chronic disease. Therefore the nomogram to determine %CRF, will be used as a risk assessment tool in this study.

A systematic search was performed with Medline and Scopus data banks from 1950 to present. The key words used were: cardiovascular disease, women, pre-menopause, obesity, visceral obesity, dyslipidemia, metabolic syndrome, physical activity, cardiorespiratory fitness, nomogram, predicted exercise capacity and the Framingham risk score. Then, many various combinations were preformed with these key words. However, to the best of our knowledge no studies have been performed to investigate the relationships between the anthropometric and body composition indices, lipid profile and the % predicted cardiorespiratory fitness in asymptomatic pre-menopausal women.

B. PURPOSE

To investigate the relationships between the percentage of predicted cardiorespiratory fitness for a given age and the anthropometric and metabolic cardiovascular disease risk factors in asymptomatic pre-menopausal women. Also, to determine if the percentage of predicted cardiorespiratory fitness for a given age is an independent determinant of the inter-individual variation observed in anthropometric and metabolic cardiovascular disease risk factors. Finally, if %CRF is a better predictor of CVD risk factors than VO_2 peak, in asymptomatic pre-menopausal women.

C. HYPOTHESIS

Primary Hypothesis: The percentage of predicted cardiorespiratory fitness will be inversely associated with body fat, visceral adipose tissue, lipid profile (TC, TG, LDL-C) and insulin sensitivity index.

Secondary Hypothesis: The percentage of predicted cardiorespiratory fitness is an independent determinant of the inter-individual variation observed in anthropometric and metabolic cardiovascular disease risk factors.

Tertiary Hypothesis: The percentage of predicted cardiorespiratory fitness is a better determinant of cardiovascular disease risk factors than the VO_2 peak.

D. LIMITATIONS

There are several possible limitations to this study. First, the cohort is only composed of asymptomatic pre-menopausal women, therefore our findings are limited only to the population studied. Second, the methods of this study are limited to the Montreal-Ottawa New Emerging Team (MONET) protocol: stress test (VO_2 peak), body composition (DEXA, CT scan) and blood sampling, all were assumed valid measurements. Third, the data analysed is limited to the baseline data collected in the longitudinal MONET study and were assumed valid. Fourth, in our pre-menopausal sample there are a small number of participants with a % of predicted cardiorespiratory fitness less than 85% for their age. Fifth, we used a crosssectional approach, which does not allow us to draw conclusions as to causal association between % CRF and anthropometric and metabolic cardiovascular disease risk factors.

CHAPTER 3

A. METHOD

Methods used in the present study are detailed in the article format within the methodology section of the article in chapter 4 entitled: **Relationship Between the Percentage of Predicted Cardiorespiratory Fitness and Cardiovascular Disease Risk Factors in Pre-menopausal Women: A MONET Study.**

CHAPTER 4

Article

This chapter presents the major findings as well as the analysis and the discussion of the results of the present study. They are presented in article format entitled: **Relationship Between the Percentage of Predicted Cardiorespiratory Fitness and Cardiovascular Disease Risk Factors in Pre-menopausal Women: A MONET Study.**

A. Relationship Between the Percentage of Predicted Cardiorespiratory Fitness and Cardiovascular Disease Risk Factors in Pre-menopausal Women: A MONET Study

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1. ABSTRACT

OBJECTIVE: To determine the relationships between the percentage predicted cardiorespiratory fitness (%CRF) and the anthropometric and metabolic cardiovascular disease risk factors in asymptomatic pre-menopausal women. METHODS: Data are baseline values obtained in 97 pre-menopausal women (age: 49.9 ± 1.9 yrs; BMI: 23.2 ± 2.2 kg/m^2) participating in a longitudinal study from 2004 to 2009. Outcome measures: VO_2 peak, body mass index (BMI), body composition [%fat, fat mass (FM), fat-free mass (FFM)], waist circumference, abdominal subcutaneous adipose tissue (ScAT), visceral AT (VAT), resting blood pressure and fasting lipids, glucose and insulin levels. RESULTS: %CRF was significantly associated with BMI, FM, %fat, waist circumference, ScAT, VAT, triglycerides, triglycerides/HDL-C, total cholesterol, total cholesterol/HDL-C and fasting insulin levels ($-0.59 > r < 0.31$; $0.01 > P < 0.05$). The stepwise multiple regression analysis showed that %CRF was only independently correlated with plasma triglyceride levels. CONCLUSION: The results of this study suggest that %CRF was not a major predictor of anthropometric and metabolic variables associated with an increased risk of cardiovascular disease in women. Finally, the use of the %CRF over VO_2 peak needs further studies.

Keywords: cardiorespiratory fitness, cardiovascular disease, body composition, metabolic profile, pre-menopausal women

2. INTRODUCTION

Cardiovascular disease (CVD) is the first cause of mortality among women in developed countries (Bittner, 2002). Many risk factors related to CVD have been identified such as abdominal obesity, physical inactivity, diabetes, hypertension, hypercholesterolemia and smoking (Bittner, 2002; Pearson, 1999). Studies showed that regular physical activity, independently of changes in body composition, decreases the risk of mortality in lean and obese individuals in primary and secondary prevention setting because of its beneficial effect on CVD risk factors (Hu *et al.*, 2005; American College of Sports Medicine, 2006).

It has been demonstrated that the risk of CVD is inversely proportional to the level of regular physical activity. Exercise guidelines recommend doing at least 30 minutes of either light or moderate physical activity on most days of the week for health improvements (Lee *et al.*, 2001; American College of Sports Medicine, 2006). Regular physical activity is associated with increases in cardiorespiratory fitness (CRF), which is another important and independent predictor of CVD, cardiac events and death among asymptomatic women (Blair *et al.*, 2001; Gulati *et al.*, 2005). A study by Lynch *et al.* (2002) demonstrated that post-menopausal women displaying a lower CRF compared to pre-menopausal and perimenopausal women of similar age and adiposity have a higher risk of CVD. Fat accumulation is another important factor associated with CVD. Among different fat depots, visceral adipose tissue (VAT) has been proven to play an important role in the development of CVD due its adverse effects on the metabolic profile (Eckel *et al.*, 2005; Williams *et al.*, 1997; Després, 2006).

A nomogram has been developed by Gulati *et al.*, (2005) to predict the risk of CVD mortality using the predicted CRF based on the age of both asymptomatic and symptomatic women. A total of 5721 asymptomatic and 4471 symptomatic women aged between 34 and 93 years underwent a symptom limited maximal stress test. Then, a linear regression equation was computed to predict the CRF in metabolic equivalent (MET) based on age in an asymptomatic cohort of women [MET = 14.7 – (0.13 x age)]. The authors reported that the risk of mortality in asymptomatic women with a percentage of predicted CRF (%CRF) < 85% of their age was two times higher than those with a %CRF ≥ 85%. To the best of our knowledge, no study has yet investigated the relationship between %CRF (a prognostic indicator of CVD) and anthropometric and metabolic cardiovascular risk factors in asymptomatic pre-menopausal women.

The goal of the present study was thus to investigate the association between the %CRF for a given age and anthropometric and metabolic cardiovascular risk factors in pre-menopausal women. Furthermore, we wanted to determine if the %CRF is 1) an independent determinant of the inter-individual variation observed in anthropometric and metabolic CVD risk factors and 2) a better predictor of CVD risk factors than VO_2 peak.

3. METHOD

3.1. Participants

The study was composed of 97 pre-menopausal women aged between 47 and 55 years participating in a longitudinal study from 2004 to 2009 on the effect of the menopause transition on body composition and cardiovascular risk factors. Due to the purpose of the study, only baseline results were used.

Pre-menopausal women were included if they meet the following criteria: pre-menopausal status (two menstruations in the last three months, no increase in cycle irregularity in the 12 months preceding testing, and a plasma follicular-stimulating hormone level < 30 IU/liter), no surgically-induced menopause, non-smoking, BMI between 20 and 29 kg/m^2. Exclusion criteria were: pregnant women or who plan to become pregnant, taking oral contraceptives or hormone replacement therapy, risk of hysterectomy and history of drug and/or alcohol abuse. This study received approval from the University of Ottawa and Montfort Hospital Ethics committees, and written consent was obtained from each participant.

3.2. Cardiorespiratory Fitness (VO_2 peak)

A progressive exercise stress test was performed to measure participants' peak maximal oxygen consumption (VO_2 peak) on a treadmill. The progressive test consisted of 3-minute stages on a treadmill with an increasing workload to the point of exhaustion. Heart rate (HR), blood pressure (BP) and the Borg scale (Borg, 1982) were taken at rest and at the end of each stage during the test. Participants were asked to refrain from any vigorous exercise and consumption of alcoholic beverages for 6 hours before the test.

They were also asked to abstain from eating and drinking coffee for 2 hours prior to the test.

A brief warm up was done prior the test. The test protocol was terminated when at least 2 of the following criteria were achieved (American College of Sports Medicine, 2006): 1) predicted maximal heart rate reached, 2) respiratory quotient > 1.1, 3) oxygen consumption remained stable or decreased with an increase in workload, or 4) rate of Borg-type scale reached ≥19. Peak oxygen consumption was considered as the highest VO_2 reached during the test. Breath-by-breath samples of expired air were collected using a mouthpiece throughout the test, and measurements of VO_2 and VCO_2 were made automatically using a Vmax 229 series metabolic cart (SensorMedics Corporation, Yorba Linda, CA).

3.3. Nomogram

The nomogram developed by Gulati *et al.* (2005) was used to predict the %CRF based on age and the CRF in MET [MET = 14.7 – (0.13 x age)]. A result equal or higher than 100%, indicates an excellent CRF in a subject. Conversely, any result lower than 100% indicates "some degree of functional impairment" (Gulati *et al.*, 2005).

3.4. Anthropometric assessment

Body weight and height were measured with a BWB-800AS digital scale and a Tanita HR-100 height rod, respectively (Tanita Corporation of America, Inc) and BMI was calculated [body weight kg/height (m^2)]. Waist circumference (mean of two

measures) was determined using a Gulick tape at the mid-distance between the lowest rib and the iliac crest.

Fat mass (FM), % fat and fat free mass (FFM) were measured using dual-energy x-ray absorptiometry (GE-LUNAR Prodigy module, GE Medical Systems, Madison, Wi, USA). Abdominal subcutaneous adipose tissue (ScAT) and visceral adipose tissue (VAT) were measured by computed tomography (GE High Speed Advantage CT Scanner, General Electric Medical Systems, Milwaukee, WI), as previously described (Doucet *et al.*, 2008). Subjects wore a light hospital gown without shoes for these measurements.

3.5. Oral glucose tolerance test

An oral glucose tolerance test (OGTT) (75g of glucose) was performed (Clark *et al.*, 2003) and plasma glucose and insulin concentration were collected, every 30 minutes, for two hours following ingestion. Insulin sensitivity index (SI_{is}OGTT) derived from OGTT was then calculated with the following equation: 1/[log(sum glucose $t_{0\text{-}30\text{-}90\text{-}120}$)(mmol/l) + log(sum insulin $t_{0\text{-}30\text{-}90\text{-}120}$)(μUI/ml)] (Bastard, *et al.*, 2007).

3.6. Blood sampling

A catheter (cathlon IV gauge 20, 1¼ inch length) was inserted by a registered nurse in antecubital vein of the forearm. Samples were taken at fast during the morning hour between 8:00 and 8:30 am, to measure the plasma lipids, insulin and glucose levels. Blood samples for plasma glucose and insulin were collected in tubes containing EDTA and stored at 4 °C. Then, samples were centrifuged at 3500 rpm at the end of each test and stored at -80 °C until they were analyzed. Plasma insulin concentrations were

determined by a 2-site ELISA immunoassay using 2 monoclonal antibodies (Linco Research, St. Louis, MO). Plasma glucose levels were determined using spectrophotometric analysis after conversion of glucose to glucose-6-phosphate by hexokinase. Laboratory-grade reagents (Sigma-Aldrich Canada Ltd., Oakville, ON; Fisher Scientific Limited, Nepean, ON) were used for preparing the hexokinase reaction. Total cholesterol (TC), high-density-lipoproteins cholesterol (HDL-C), and triglycerides (TG) were analyzed using the Vitros 950 immunoassay analyzer (Ortho Clinical Diagnostics, Johnson & Johnson Company) at a wavelength of 540 nm. TC, HDL-C, and TG were used in the Friedewald formula (Friedewald *et al.*, 1972) to calculate low-density-lipoproteins cholesterol (LDL-C) concentration.

3.7. Statistical analysis

Results are expressed as the mean ± standard deviation. Pearson correlations were used to determine the association between the predicted %CRF value and the various dependent variables of interest. Stepwise multiple regression analyses were used to identify independent predictors CVD risk factors. Finally, independent-sample T-tests were used to compare CVD risk factors means between subjects with a high *vs.* a low %CRF. A P value ≤ 0.05 was considered as significant. Statistical analyses were done using SPSS 15.0 for windows (SPSS Inc. Chicago, Illinois, USA).

4. RESULTS

The characteristic of the 97 asymptomatic pre-menopausal women are presented in Tables 1 and 2. To the exception of age, our cohort displayed a broad range of values for the variables of interest. Furthermore, the %CRF ranged between 70.6% and 147.7%. Also, 12.4%, 29.9% and 57.7% of the participants had a %CRF < 85%, between 85 and 100% and > 100%, respectively.

Insert Table1 and 2

Persons' correlations between fitness measures (%CRF and peak VO_2) and dependent variables of interest are presented in Table 3. %CRF was negatively associated with BMI, FM, % fat, WC, ScAT and VAT areas ($-0.24 \geq r \leq -0.59$; $P < 0.01$). %CRF was also negatively associated ($-0.20 \geq r \leq -0.39$; $P < 0.05$) with fasting plasma TG, TC, TG/HDL-C, ratio, TC/HDL-C ratio and insulin, and positively correlated with the insulin sensitivity index measured during the OGTT ($SI_{is}OGTT$) ($r = 0.23$, $P < 0.05$). As for the VO_2 peak, correlations were slightly better compared to %CRF, particularly for anthropometric measurements ($-0.70 \geq r \leq 0.30$; $P < 0.05$). Finally, peak VO_2 was also significantly correlated with body weight ($r = -0.31$, $P < 0.01$) and fasting LDL-C ($r = -0.25$, $P < 0.05$).

Insert Table 3

Stepwise multiple regression analyses were done to examine if the %CRF and/or VO_2 peak were independent predictors of CVD risk factors. For each dependent variable, %CRF, VO_2 peak and all other anthropometric and/or metabolic factors that were significantly correlated were added to the model as independent variables. As a result, %CRF was only independently correlated with plasma TG levels. Overall, %CRF, TC and insulin sensitivity index explaining 36% of the variance observed for plasma TG levels ($P < 0.001$) (Table 4).

Insert Table 4

Finally, independent sample t-tests (table 5) were performed to compare pre-menopausal women with high >85% vs. low <85% %CRF. Compared to subjects with a high %CRF, those with low a %CRF had a lower VO_2 peak and higher values for BMI, % fat, FM, ScAT, VAT, fasting plasma TG and insulin levels ($0.05 < P < 0.01$).

Insert Table 5

5. DISCUSSION

The present study is, to our knowledge, the first to report significant associations between the %CRF and anthropometric and metabolic CVD risk factors in pre-menopausal women. Our results demonstrate that %CRF was negatively correlated with CVD risk factors such as BMI, WC, FM, % fat, TG and TG/HDL-C ratio. Also, our results showed that fasting plasma insulin and the insulin sensitivity index ($SI_{is}OGTT$) were significantly associated with %CRF. However, based on regression analyses, %CRF was not a significant predictor for any CVD risk factor (data not shown), with the exception of plasma TG levels. We found that %CRF, TC and $SI_{is}OGTT$ explained together 36% of the variance observed in plasma TG levels in our sample of pre-menopausal women (table 4). As, it was reported that TG and HDL-C plasma levels are considered strong predictors of CVD among women (Bitner, 2005) and that these lipids are positively affected by regular physical activity and improvements in VO_2 peak (Major *et al.*, 2005; Durstine *et al*,. 1994). Moreover, when we compared the correlations between %CRF, VO_2 peak and anthropometric and metabolic variables, the associations were, in general, slightly better with VO_2 peak (table 3). Also, according to the regression analysis VO_2 peak was among the independent predictors only for BMI, % fat and FM (data not shown). These results suggest that %CRF could be an indirect correlate of CVD risk factors.

Cardiorespiratory fitness is a valid proxy of functional capacity of the cardiorespiratory system measured by maximal and/or peak oxygen consumption (Heyward, 2006). CRF can be influenced either by regular physical activity, genetic factors or both (Bouchard *et al.*, 1998). High CRF has been independently associated

with a reduced risk of metabolic disturbances (Vainiopää *et al.*, 2007), while a high %CRF was associated with a reduced risk of unstable angina and myocardial infarction among asymptomatic women (Gulati *et al.*, 2005; Peterson *et al.*, 2008). It has been reported that women with a low %CRF (< 85% of age-predicted peak maximal CRF value) presented a 2.44 fold risk of mortality from cardiac causes compared to those with a high %CRF (> 85% of age-predicted peak maximal CRF value) (Gulati *et al.*, 2005). In our sample, 12.4% of the participants had a fitness level lower than 85% of age-predicted peak maximal CRF, which is lower than the 21% reported by Peterson *et al.* (2008). One possible reason to explain the lower prevalence in our sample can be the different inclusion criteria used and a different population. In our cohort we included relatively lean and healthy pre-menopausal women whereas overweight and obese pre- and post-menopausal women were included in the study by Peterson *et al.* (2008). Furthermore, our results indicated that, women with a low %CRF have a higher FM, % fat, ScAT, VAT, TG and fasting insulin and a lower VO_2 peak compared to women with high %CRF. These results support and extend the classical knowledge that fit subjects have a lower CVD risk than unfit subjects (Jetté *et al.,* 1992; Vainiopää *et al.*, 2007; Haddock *et al.*, 1998).

These results, as well as the high correlation observed between %CRF and VO_2 peak ($r=0.85$, $P<0.001$) could then question the clinical importance to measure the %CRF in addition of the VO_2 peak to determine asymptomatic pre-menopausal women at higher risk of cardiovascular disease. This is further supported by the fact that many studies have shown that a lower VO_2 max is associated with an increased risk of CVD (Blair *et al.*, 2001). Furthermore, even after adjustment for adiposity or fat distribution, fitness

remained a predictor for mortality (Sui et al., 2007). Nevertheless, there is no indication in the literature that VO_2 peak is a better CVD predictor than %CRF. In fact, Gulati *et al.* (2005) and Peterson *et al.* (2008) did not provide any results on whether %CRF is a better predictor of cardiovascular events and mortality than the VO_2 peak in their respective population.

Our study presents some limitations. First, the population studied was composed of relatively lean and healthy women. Thus our findings are limited to this population. Second, only a small number of participants present a %CRF less than 85% for age. Third, we used a cross-sectional approach, which does not allow us to draw conclusions as to causal association between % CRF and anthropometric and metabolic cardiovascular disease risk factors. Despite these limitations, the present study is strengthened by the well-characterized cohort of pre-menopausal women. We used gold standard measures methods (DEXA and CT scan) for the measurement of body composition. Second, VO_2 peak is a valid and highly reproducible measure of CRF (Vanhees *et al.*, 2005). Finally, to the exception of age, our cohort displayed a broad range of values for the variables of interest.

In summary, the results of this study suggest that %CRF was not a major predictor of anthropometric and metabolic variables associated with an increased risk of cardiovascular disease in women. Finally, studies are however needed to investigate the potential independent contribution of %CRF and VO_2 peak measurements in individuals at higher risk for cardiovascular disease.

6. REFERENCES

American College of Sports Medicine 2006, ACSM's guidelines for exercise testing and prescription, 7th edn, Lippincott Williams & Wilkins, Baltimore.

Bastard, J.P., Vandernotte, J.M., Faraj, M., Karelis, A.D., Messier, L., Malita, F.M., Garrel, D., Prud'homme, D. & Rabasa-Lhoret, R. 2007, "Relationship between the hyperinsulinemic-euglycaemic clamp and a new simple index assessing insulin sensitivity in overweight and obese postmenopausal women", *Diabetes and Metabolism,* vol. 33, no. 4, pp. 261-268.

Bittner, V. 2002, "Women and cardiovascular disease risk factors", *Journal of Cardiovascular Risk,* vol. 9, no. 6, pp. 315-322.

Bittner, V. 2005, "Perspectives on dyslipidemia and cardiovascular disease in women", *Journal of the American College of Cardiology,* vol. *46,* no. 9, pp. 1628-1635.

Blair, S.N. & Jackson, A.S. 2001, "Physical fitness and activity as separate heart disease risk factors: A meta-analysis", *Medicine and Science in Sports and Exercise,* vol. 33, no. 5, pp. 762-764.

Borg, G. A. V. (1982). Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise, 14*(5), 377-381.

Bouchard, C., Warwick Daw, E., Rice, T., Pérusse, L., Gagnon, J., Province, M.A., Leon, A.S., Rao, D.C., Skinner, J.S. & Wilmore, J.H. 1998, "Familial resemblance for VO(2max) in the sedentary state: The HERITAHE family study", *Medicine and Science in Sports and Exercise,* vol. 30, no. 2, pp. 252-258.

Clark, H.D., Van Walraven, C., Code, C., Karovitch, A. & Keely, E. 2003, "Did publication of a clinical practice guideline recommendation to screen for type 2 diabetes in women with gestational diabetes change practice?", *Diabetes Care,* vol. 26, no. 2, pp. 265-268.

Després, J.P. 2006, "Is visceral obesity the cause of the metabolic syndrome?", *Annals of Medicine,* vol. 38, no. 1, pp. 52-63.

Doucet, E., Laviolette, M., Imbeault, P., Strychar, I., Rabasa-Lhoret, R. & Prud'homme, D. 2008, "Total peptide YY is a correlate of postprandial energy expenditure but not of appetite or energy intake in healthy women", *Metabolism: Clinical and Experimental,* vol. 57, no. 10, pp. 1458-1464.

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

Eckel, R.H., Grundy, S.M. & Zimmet, P.Z. 2005, "The metabolic syndrome", *Lancet,* vol. 365, no. 9468, pp. 1415-1428.

Friedewald, W.T., Levy, R.I. & Fredrickson, D.S. 1972, "Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge.", *Clinical Chemistry,* vol. 18, no. 6, pp. 499-502.

Gulati, M., Black, H.R., Shaw, L.J., Arnsdorf, M.F., Merz, C.N.B., Lauer, M.S., Marwick, T.H., Pandey, D.K., Wicklund, R.H. & Thisted, R.A. 2005, "The prognostic value of a nomogram for exercise capacity in women", *New England Journal of Medicine,* vol. 353, no. 5, pp. 468-475.

Haddock, B.L., Hopp, H.P., Mason, J.J., Blix, G. & Blair, S.N. 1998, "Cardiorespiratory fitness and cardiovascular disease risk factors in postmenopausal women", *Medicine and Science in Sports and Exercise,* vol. 30, no. 6, pp. 893-898.

Heyword, V.H. 2006, "Assessing Cardiorespiratory Fitness" in *Advanced Fitness Assessment and Exercise Prescription*, Fifth edn, Human Kinetics, Champaign, IL, pp. 55.

Hu, G., Tuomilehto, J., Silventoinen, K., Barengo, N.C., Peltonen, M. & Jousilahti, P. 2005, "The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47 212 middle-aged Finnish men and women", *International Journal of Obesity,* vol. 29, no. 8, pp. 894-902.

Jette, M., Sidney, K., Quenneville, J. & Landry, F. 1992, "Relation between cardiorespiratory fitness and selected risk factors for cardiovascular disease in a population of Canadian men and women", *Canadian Medical Association Journal,* vol. 146, no. 8, pp. 1353-1360.

Lee, I.-., Rexrode, K.M., Cook, N.R., Manson, J.E. & Buring, J.E. 2001, "Physical activity and coronary heart disease in women: Is "No Pain, No Gain" passé?", *Journal of the American Medical Association,* vol. 285, no. 11, pp. 1447-1454.

Lynch, N.A., Ryan, A.S., Berman, D.M., Sorkin, J.D. & Nicklas, B.J. 2002, "Comparison of VO2max and disease risk factors between perimenopausal and postmenopausal women", *Menopause,* vol. 9, no. 6, pp. 456-462.

Major, G. C., Piché, M. -., Bergeron, J., Weisnagel, S. J., Nadeau, A., & Lemieux, S. 2005, "Energy expenditure from physical activity and the metabolic risk profile at menopause", *Medicine and Science in Sports and Exercise,* vol. *37,* no. 2, pp. 204-212.

Peterson, P. N., Magid, D. J., Ross, C., Ho, P. M., Rumsfeld, J. S., Lauer, M. S., et al. 2008. "Association of exercise capacity on treadmill with future cardiac events in patients referred for exercise testing", *Archives of Internal Medicine,* vol. 168, no.2, pp. 174-179.

Pearson, T. A. 1999, "Cardiovascular disease in developing countries: Myths, realities, and opportunities", *Cardiovascular Drugs & Therapy,* vol. 13, no 2, pp. 95-104.

Sui, X., LaMonte, M.J., Laditka, J.N., Hardin, J.W., Chase, N., Hooker, S.P. & Blair, S.N. 2007, "Cardiorespiratory fitness and adiposity as mortality predictors in older adults", *Journal of the American Medical Association,* vol. 298, no. 21, pp. 2507-2516.

Vainionpää, A., Korpelainen, R., Kaikkonen, H., Knip, M., Leppäluoto, J. & Jämsä, T. 2007, "Effect of impact exercise on physical performance and cardiovascular risk factors", *Medicine and Science in Sports and Exercise,* vol. 39, no. 5, pp. 756-763.

Vanhees, L., Lefevre, J., Philippaerts, R., Martens, M., Huygens, W., Troosters, T., et al. 2005, "How to assess physical activity? how to assess physical fitness", *European Journal of Cardiovascular Prevention and Rehabilitation,* vol. 12, no. 2, pp. 102-114.

Williams, M.J., Hunter, G.R., Kekes-Szabo, T., Snyder, S. & Treuth, M.S. 1997, "Regional fat distribution in women and risk of cardiovascular disease.[see comment]", *American Journal of Clinical Nutrition,* vol. 65, no. 3, pp. 855-860.

Table 1. Anthropometric and Metabolic Characteristics of the Pre-menopausal Women.

Variable	N	Mean±SD	Min	Max
Age (yrs)	97	49.9±1.9	47	55
Height (cm)	97	161.9±6.2	150.0	180.5
Weight (kg)	97	60.9±6.7	46.8	79.7
BMI (kg/m²)	97	23.2±2.2	19.3	28.7
% fat	97	31.1±6.5	18.2	42.4
Fat free mass (kg)	97	39.1±4.1	31.2	50.1
Fat mass (kg)	97	19.1±5.4	9.6	31.5
WC (cm)	97	77.9±6.6	62.2	93.7
Abdominal AT.				
- Subcutaneous (cm²)	88	223.2±71.2	87.0	382.0
- visceral (cm²)	88	48.4±25.0	11.8	125.1
TG (mmol/l)	96	0.9±0.3	0.4	2.4
TC (mmol/l)	96	4.5±0.7	3.1	6.2
HDL-C (mmol/l)	96	1.6±0.4	0.8	2.7
LDL-C (mmol/l)	96	2.5±0.6	1.3	4.3
TC/HDL-C	96	3.0±0.7	1.8	5.4
TG/HDL	96	0.6±0.3	0.3	2.1
Fasting Glucose (mmol/l)	97	4.8±0.4	3.8	5.7
Fasting Insulin (pmol/l)	97	20.3±9.9	1.2	53.5
$SI_{is}OGTT$	95	0.31 ± 0.02	0.26	0.40

AT: adipose tissue; BMI: body mass index; HDL-C: high-density-lipoproteins cholesterol; LDL-C: low density lipoproteins cholesterol; N: number of subjects; SD: standard deviation; $SI_{is}OGTT$: insulin sensitivity index; TC: total cholesterol; TG: triglycerides; WC: waist circumference.

Table 2. Physiological Characteristics of the Pre-menopausal Women.

Variable	N	Mean±SD	Min	Max
VO_2 peak ($mlO_2 \cdot kg^{-1} \cdot min^{-1}$)	97	33.8±5.9	20.9	52.0
% Predicted CRF	97	103.0±14.5	70.6	147.7
Maximal Heart rate (bpm)	97	172.9±9.9	149	196
% Heart rate predicted for age	97	101.6±5.9	87.7	117.4
Resting BP				
Systolic (mm Hg)	97	115.4±11.5	88	148
Diastolic (mm Hg)	97	72.9±8.1	40	90
Maximal BP during exercise				
Systolic (mm Hg)	96	171.5±17.6	136	248
Diastolic (mm Hg)	96	72.9±8.5	56	98

BP: blood pressure; bpm: beat per minute; CRF: cardiorespiratory fitness; N: number of subjects; SD: standard deviation.

Table 3. Correlations between measures of fitness level and dependent anthropometric and metabolic measures of interest.

	%CRF	VO_2peak
Weight	-0.16	-0.31**
BMI	-0.34**	-0.50**
% Fat	-0.59**	-0.70**
FM	-0.47**	-0.61**
WC	-0.24*	-0.37**
Adipose Tissue		
Subcutaneous	-0.31**	-0.41**
Visceral	-0.38**	-0.45**
Resting BP		
Systolic	0.05	0.03
Diastolic	-0.04	-0.10
TG	-0.39**	-0.40**
TC	-0.20*	-0.25*
HDL-C	0.09	0.12
LDL-C	-0.18	-0.25*
TC/HDL-C	-0.25*	-0.32**
TG/HDL-C	-0.37**	-0.39**
Fasting Glucose	-0.12	-0.13
Fasting Insulin	-0.31**	-0.28**
SI_{is}OGTT	0.23*	0.30**

** $P \leq 0.01$;* $P \leq 0.05$.

BMI: body mass index; BP: blood pressure; FM: fat mass; HDL-C: high-density-lipoproteins cholesterol; LDL-C: low-density-lipoproteins cholesterol; SI_{is}OGTT: insulin sensitivity index; TC: total cholesterol; TG: triglycerides; VO_2 peak: peak oxygen consumption ($mlO_2 \cdot kg^{-1} \cdot min^{-1}$); WC: waist circumference; %CRF: percentage predicted cardiorespiratory fitness

Table 4. Stepwise regression analysis regarding the inter-individual variation observed in plasma triglycerides levels.

Dependent variable	Independent variable	R^2 change	P value	Total
Plasma TG	TC	0.23	< 0.001	0.36
	%CRF	0.09	< 0.01	
	$SI_{is}OGTT$	0.04	< 0.05	

AT: adipose tissue; $SI_{is}OGTT$: insulin sensitivity index; TC: total cholesterol; TG: triglycerides; %CRF: percentage predicted cardiorespiratory fitness. Model included: peak oxygen consumption ($mlO_2 \cdot kg^{-1} \cdot min^{-1}$), %CRF, body mass index, % fat, waist circumference, visceral AT, Total AT, $SI_{is}OGTT$, plasma insulin and TC.

Table 5. Comparison of anthropometric and metabolic characteristics of pre-menopausal women with low (< 85%) vs. high (> 85%) of predicted cardiorespiratory fitness.

Variables	% of predicted cardiorespiratory fitness	
	Low (< 85%) Mean±SD	High (>85%) Mean±SD
N	12	85
BMI (kg/m²)	24.7±1.3	23.0±2.2**
% fat	38.9±2.4	30.0±6.2**
Fat mass (kg)	24.6±3.3	18.3±5.2**
WC (cm)	80.5±4.9	77.6±6.8
Abdominal AT (cm²)		
Subcutaneous	272.6±58.7	215.4±70.2**†
Visceral	69.1±18.0	45.1±24.4**†
VO_2 peak ($mlO_2 \cdot kg^{-1} \cdot min^{-1}$)	26.3±3.0	34.9±5.4**
TG (mmol/l)	1.08±0.5	0.83±0.3*
TC (mmol/l)	4.63±0.5	4.43±0.7
HDL-C (mmol/l)	1.48±0.4	1.57±0.3
LDL-C (mmol/l)	2.66±0.6	2.46±0.6
TC/HDL-C	3.40±1.0	2.90±0.7
Fasting glucose (mmol/l)	4.93±0.5	4.80±0.4
Fasting insulin (pmol/l)	26.1±14.1	19.5±9.0*
$SI_{is}OGTT$	0.31±0.2	0.31±0.2

** $P \leq 0.01$; * $P \leq 0.05$.

† n= 76

BMI: Body Mass Index; HDL-C: High-Density-Lipoproteins cholesterol; LDL-C: Low-Density-Lipoproteins cholesterol; N: number of subjects; SD: standard deviation; TC: Total Cholesterol; TG: Triglycerides; VO_2 peak: peak oxygen consumption; WC: Waist Circumference.

CHAPTER 5

A. CONCLUSIONS AND PERSPECTIVES

Altogether, the literature reveals that cardiovascular disease affects both women and men, and is the leading cause of mortality in both men and women altogether. Many risk factors have been described: obesity, abdominal obesity, dyslipidemia, insulin resistance, type 2 diabetes etc (6). Prevalence of these CVD risk factors tends to increase as women age especially at menopause (7). Physical activity levels and CRF have been proven to attenuate the risk of cardiovascular disease in women with risk factors independent of age and BMI (69, 92, 127). Likewise, a number of valid CVD risk assessment tools have been created to identify and recommend preventive treatment for individuals at high risk for cardiovascular disease. Some tools use a combination of risk factors such as the metabolic syndrome (50) and the Framingham score (111), as opposed to a single indicator as the nomogram of the % predicted cardiorespiratory fitness (19). Of the three, the nomogram developed by Gulati *et al.* (19) was used in this study because it has been reported that %CRF predicted for age, is a good predictor to identify asymptomatic women at risk for cardiovascular disease (19).

The objective of the present study was three-fold. First, to investigate the relationships between the % CRF and the anthropometric and metabolic cardiovascular disease risk factors; second, to determine if the % CRF is major predictor of the anthropometric and metabolic CVD risk factors; third to determine if %CRF is a better predictor of CVD risk factors than VO_2 peak. The main findings suggest that women with a low % CRF present a higher BMI, % fat, FM, ScAT, VAT, TG, and lower insulin

sensitivity then women with a higher %CRF. Furthermore, %CRF was not a major determinant of the inter-individual variation in anthropometric and metabolic cardiovascular disease risk factors in asymptomatic pre-menopausal women, except for plasma triglycerides. Moreover, when we compared the correlation between %CRF, VO_2 peak with anthropometric and metabolic variables, the results were, in general, slightly higher with VO_2 peak. However VO_2 peak was not a better predictor of CVD risk factor than %CRF based on the multiple regression analysis. These results suggest that further studies are needed to verify the superiority prognostic value of %CRF over VO_2 peak measurement for identifying women at higher risk of cardiovascular disease. Also it would be of great interest to compare the %CRF to other CVD risk assessment tools such as the metabolic syndrome and the Framingham score to identify and recommend preventive treatment for women at high risk for cardiovascular disease. In addition, it would be of great interest to investigate the effect of the menopause transition on the % cardiorespiratory fitness and to determine if pre-menopausal women with a low %CRF would show higher cardiovascular disease risk deterioration during the menopause transition.

REFERENCES

1 Pearson, T. A. (1999). Cardiovascular disease in developing countries: Myths, realities, and opportunities.[see comment]. *Cardiovascular Drugs & Therapy, 13*(2), 95-104.

2 WORLD HEALTH ORGANIZATION. (2002). *The* WORLD HEALTH REPORT *2002 reducing risks, promoting healthy life.*

3 Dougherty, P. L., Faucher, M. A., Gillman, P. H., Taubenheim, A. M., Wilton, J. M., & Woodson, S. A. (2006). Cardiovascular disease. why women need to get serious about heart health now. *AWHONN Lifelines, 10*(5), 390-398.

4 Mosca, L., Ferris, A., Fabunmi, R., & Robertson, R. M. (2004). Tracking women's awareness of heart disease: An american heart association national study. *Circulation, 109*(5), 573-579.

5 Murphy, B., Worcester, M., Higgins, R., Le Grande, M., Larritt, P., & Goble, A. (2005). Causal attributions for cardiovascular disease among female cardiac patients.[see comment]. *Journal of Cardiopulmonary Rehabilitation, 25*(3), 135-143.

6 Bittner, V. (2002). Women and cardiovascular disease risk factors. *Journal of Cardiovascular Risk, 9*(6), 315-322.

7 Wenger, N. K., Speroff, L., & Packard, B. (1993). Cardiovascular health and disease in women. *New England Journal of Medicine, 329*(4), 247-256.

8 Manolio, T. A., Pearson, T. A., Wenger, N. K., Barrett-Connor, E., Payne, G. H., & Harlan, W. R. (1992). Cholesterol and heart disease in older persons and women. review of an NHLBI workshop.[see comment]. *Annals of Epidemiology, 2*(1-2), 161-176.

9 Mokdad, A. H., Ford, E. S., Bowman, B. A., Dietz, W. H., Vinicor, F., & Bales, V. S., et al. (2003). Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA, 289*(1), 76-79.

10 Mokdad, A. H., Marks, J. S., Stroup, D. F., & Gerberding, J. L. (2004). Actual causes of death in the united states, 2000.[see comment][erratum appears in JAMA. 2005 jan 19;293(3):293-4; PMID: 15657315]. *JAMA, 291*(10), 1238-1245.

11 Mokdad, A. H., Bowman, B. A., Ford, E. S., Vinicor, F., Marks, J. S., & Koplan, J. P. (2001). The continuing epidemics of obesity and diabetes in the united states. *Journal of the American Medical Association, 286*(10), 1195-1200.

12 Fujioka, S., Matsuzawa, Y., Tokunaga, K., & Tarui, S. (1987). Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism: Clinical & Experimental, 36*(1), 54-59.

13 Regitz-Zagrosek, V., Lehmkuhl, E., & Weickert, M. O. (2006). Gender differences in the metabolic syndrome and their role for cardiovascular disease.[erratum appears in clin res cardiol. 2006 mar;95(3):147]. *Clinical Research in Cardiology, 95*(3), 136-147.

14 Murtagh, J. (2003). Dyslipidaemia. ***General practice*** (Third ed., pp. 1301). Australia: McGraw-Hill Companies.

15 Third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report.(2002). *Circulation, 106*(25), 3143-3421.

16 Lee, I. M., Rexrode, K. M., Cook, N. R., Manson, J. E., & Buring, J. E. (2001). Physical activity and cardiovascular disease in women: Is "no pain, no gain" passe?[see comment]. *JAMA, 285*(11), 1447-1454.

17 Canadian Society for Exercise Physiology. (2003). The Canadian Physical Activity, Fitness & Lifestyle Approach.

18 Blair, S. N., & Brodney, S. (1999). Effects of physical inactivity and obesity on morbidity and mortality: Current evidence and research issues. *Medicine & Science in Sports & Exercise, 31*(11 Suppl), S646-62.

19 Gulati, M., Black, H. R., Shaw, L. J., Arnsdorf, M. F., Merz, C. N., & Lauer, M. S., et al. (2005). The prognostic value of a nomogram for exercise capacity in women.[see comment]. *New England Journal of Medicine, 353*(5), 468-475.

20 Blair, S. N., Kohl, H. W.,3rd, Paffenbarger, R. S.,Jr, Clark, D. G., Cooper, K. H., & Gibbons, L. W. (1989). Physical fitness and all-cause mortality. A prospective study of healthy men and women.[see comment]. *JAMA, 262*(17), 2395-2401.

21 Lakka, T. A., Laaksonen, D. E., Lakka, H. M., Mannikko, N., Niskanen, L. K., & Rauramaa, R., et al. (2003). Sedentary lifestyle, poor cardiorespiratory fitness, and the metabolic syndrome. *Medicine & Science in Sports & Exercise, 35*(8), 1279-1286.

22 Lee, S., Kuk, J. L., Katzmarzyk, P. T., Blair, S. N., Church, T. S., & Ross, R. (2005). Cardiorespiratory fitness attenuates metabolic risk independent of abdominal subcutaneous and visceral fat in men. *Diabetes Care, 28*(4), 895-901.

23 NHLBI Obesity Education Initiative. (1998). ***The practical guide*** *Identification, evaluation, and treatment of overweight and obesity in adults* No. 00-4084)NIH Publication.

24 Wyshak, G. (2007). Weight change, obesity, mental health, and health perception: Self-reports of college-educated women. *Primary Care Companion to the Journal of Clinical Psychiatry, 9*(1), 48-54.

25 Lau, D. C., Douketis, J. D., Morrison, K. M., Hramiak, I. M., Sharma, A. M., & Ur, E. (2007). 2006 canadian clinical practice guidelines on the management and prevention of obesity in adults and children . *CMAJ : Canadian Medical Association Journal = Journal De l'Association Medicale Canadienne, 176*(8), 1-117.

25 Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults--the evidence report. national institutes of health.[see comment][erratum appears in obes res 1998 nov;6(6):464].(1998). *Obesity Research, 6*(Suppl 2), 51S-209S.27 Romero-Corral, A., Somers, V.K., Sierra-Johnson, J., Jensen, M.D., Thomas, R.J., Squires, R.W., Allison, T.G., Korinek, J. & Lopez-Jimenez, F. (2007). Diagnostic performance of body mass index to detect obesity in patients with coronary artery disease. *European Heart Journal,* 28(17), 2087-2093.

28 Bunout, D., Rueda, E., Aicardi, V., Hidalgo, C. & Kauffmann, R. (1994). Influence of body fat and its distribution on cardiovascular risk factors in healthy subjects. *Revista medica de Chile,* 122(2), 123-132.

29 Nakanishi, N., Nakamura, K., Suzuki, K., Matsuo, Y. & Tatara, K. (2000). Associations of body mass index and percentage body fat by bioelectrical impedance analysis with cardiovascular risk factors in Japanese male office workers. *Industrial Health,* 38(3), 273-279.

30 Manson, J. E., Colditz, G. A., Stampfer, M. J., Willett, W. C., Rosner, B., & Monson, R. R., et al. (1990). A prospective study of obesity and risk of cardiovascular disease in women.[see comment]. *New England Journal of Medicine, 322*(13), 882-889.

31 Després, J. -. (2007). Cardiovascular disease under the influence of excess visceral fat. *Critical Pathways in Cardiology, 6*(2), 51-59.

32 Despres, J. P., Pouliot, M. C., Moorjani, S., Nadeau, A., Tremblay, A., & Lupien, P. J., et al. (1991). Loss of abdominal fat and metabolic response to exercise training in obese women. *American Journal of Physiology, 261*(2 Pt 1), E159-67.

33 Williams, M. J., Hunter, G. R., Kekes-Szabo, T., Snyder, S., & Treuth, M. S. (1997). Regional fat distribution in women and risk of cardiovascular disease.[see comment]. *American Journal of Clinical Nutrition, 65*(3), 855-860.

34 Després, J. -., Pascot, A., & Lemieux, I. (2000). Risk factors associated with obesity: A metabolic perspective. [Facteurs de risque associés à l'obésité: Le point de vue du métabolicien] *Annales d'Endocrinologie, 61*(6 SUPPL.), 31-38.

35 Nicklas, B. J., Penninx, B. W. J. H., Cesari, M., Kritchevsky, S. B., Newman, A. B., Kanaya, A. M., et al. (2004). Association of visceral adipose tissue with incident myocardial infarction in older men and women: The health, aging and body composition study. *American Journal of Epidemiology, 160*(8), 741-749.

36 Ferrara, C. M., Lynch, N. A., Nicklas, B. J., Ryan, A. S., & Berman, D. M. (2002). Differences in adipose tissue metabolism between postmenopausal and perimenopausal women. *Journal of Clinical Endocrinology & Metabolism, 87*(9), 4166-4170.

37 Park, H. S., & Lee, K. U. (2003). Postmenopausal women lose less visceral adipose tissue during a weight reduction program. *Menopause, 10*(3), 222-227.

38 Brochu, M., Starling, R. D., Tchernof, A., Matthews, D. E., Garcia-Rubi, E., & Poehlman, E. T. (2000). Visceral adipose tissue is an independent correlate of glucose disposal in older obese postmenopausal women. *Journal of Clinical Endocrinology & Metabolism, 85*(7), 2378-2384.

39 Colombel, A., & Charbonnel, B. (1997). Weight gain and cardiovascular risk factors in the post-menopausal women. *Human Reproduction, 12*(Suppl 1), 134-145.

40 Azizi, F., Esmaillzadeh, A., Mirmiran, P., & Ainy, E. (2005). Is there an independent association between waist-to-hip ratio and cardiovascular risk factors in overweight and obese women? *International Journal of Cardiology, 101*(1), 39-46.

41 Ozbey, N., Sencer, E., Molvalilar, S., & Orhan, Y. (2002). Body fat distribution and cardiovascular disease risk factors in pre- and postmenopausal obese women with similar BMI. *Endocrine Journal, 49*(4), 503-509.

42 Wierzbicki, A. S. (2007). Lipid-altering therapies and the progression of atherosclerotic disease. *CardioVascular and Interventional Radiology, 30*(2), 155-160.

43 Bittner, V. (2005). Perspectives on dyslipidemia and cardiovascular disease in women. *Journal of the American College of Cardiology, 46*(9), 1628-1635.

44 Mazza, A., Tikhonoff, V., Schiavon, L., & Casiglia, E. (2005). Triglycerides + high-density-lipoprotein-cholesterol dyslipidaemia, a coronary risk factor in elderly women: The CArdiovascular STudy in the ELderly. *Internal Medicine Journal, 35*(10), 604-610.

45 Hulley, S., Grady, D., Bush, T., Furberg, C., Herrington, D., & Riggs, B., et al. (1998). Randomized trial of estrogen plus progestin for secondary prevention of cardiovascular disease in postmenopausal women. heart and Estrogen/progestin replacement study (HERS) research group.[see comment]. *JAMA, 280*(7), 605-613.

46 Weiss NS. (1972). Relationship of menopause to serum cholesterol and arterial blood pressure. *American Journal of Epidemiology, 96*, 237-41.

47 Stevenson, J. C., Crook, D., & Godsland, I. F. (1993). Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis, 98*(1), 83-90.

48 Bonithon-Kopp, C., Scarabin, P. Y., Darne, B., Malmejac, A., & Guize, L. (1990). Menopause-related changes in lipoproteins and some other cardiovascular risk factors. *International Journal of Epidemiology, 19*(1), 42-48.

49 Peters, H. W., Westendorp, I. C., Hak, A. E., Grobbee, D. E., Stehouwer, C. D., & Hofman, A., et al. (1999). Menopausal status and risk factors for cardiovascular disease. *Journal of Internal Medicine, 246*(6), 521-528.

50 Dekker, J. M., Girman, C., Rhodes, T., Nijpels, G., Stehouwer, C. D., & Bouter, L. M., et al. (2005). Metabolic syndrome and 10-year cardiovascular disease risk in the hoorn study. *Circulation, 112*(5), 666-673.

51 Expert Panel on Detection, Evaluation,and Treatment of High Blood Cholesterol in Adults. (2001). Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III).[see comment]. *JAMA, 285*(19), 2486-2497.

52 DiPietro, L. (1995). Physical activity, body weight, and adiposity: An epidemiologic perspective. *Exercise and Sport Sciences Reviews, 23*, 275-303.

53 Hu, G., Tuomilehto, J., Silventoinen, K., Barengo, N. C., Peltonen, M., & Jousilahti, P. (2005). The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47 212 middle-aged finnish men and women. *International Journal of Obesity, 29*(8), 894-902.

54 Mora, S., Lee, I. -., Buring, J. E., & Ridker, P. M. (2006). Association of physical activity and body mass index with novel and traditional cardiovascular biomarkers in women. *Journal of the American Medical Association, 295*(12), 1412-1419.

55 Haapanen-Niemi, N., Miilunpalo, S., Pasanen, M., Vuori, I., Oja, P., & Malmberg, J. (2000). Body mass index, physical inactivity and low level of physical fitness as determinants of all-cause and cardiovascular disease mortality - 16 y follow-up of middle-aged and elderly men and women. *International Journal of Obesity, 24*(11), 1465-1474.

56 LaMonte, M. J., Durstine, J. L., Addy, C. L., Irwin, M. L., & Ainsworth, B. E. (2001). Physical activity, physical fitness, and framingham 10-year risk score: The cross-cultural activity participation study. *Journal of Cardiopulmonary Rehabilitation, 21*(2), 63-70.

57 Sternfeld, B., Bhat, A. K., Wang, H., Sharp, T., & Quesenberry Jr., C. P. (2005). Menopause, physical activity, and body composition/fat distribution in midlife women. *Medicine and Science in Sports and Exercise, 37*(7), 1195-1202.

58 Wofford, M. R., & Hall, J. E. (2004). Pathophysiology and treatment of obesity hypertension. *Current Pharmaceutical Design, 10*(29), 3621-3637.

59 Pascot, A., Lemieux, S., Lemieux, I., Prud'homme, D., Tremblay, A., & Bouchard, C., et al. (1999). Age-related increase in visceral adipose tissue and body fat and the metabolic risk profile of premenopausal women. *Diabetes Care, 22*(9), 1471-1478.

60 Major, G. C., Piché, M. -., Bergeron, J., Weisnagel, S. J., Nadeau, A., & Lemieux, S. (2005). Energy expenditure from physical activity and the metabolic risk profile at menopause. *Medicine and Science in Sports and Exercise, 37*(2), 204-212.

61 Poirier, P., & Despres, J. P. (2001). Exercise in weight management of obesity. *Cardiology Clinics, 19*(3), 459-470.

62 Azadbakht, L., Mirmiran, P., Shiva, N., & Azizi, F. (2005). General obesity and central adiposity in a representative sample of tehranian adults: Prevalence and determinants. *International Journal for Vitamin and Nutrition Research, 75*(4), 297-304.

63 Dansou, P., Lucrèce Kotin, M., Laleye, A., Lawani, M., & Darboux, R. (2004). Effects of physical activity on adipose tissue cellularity in premenopausal obese women in Bénin. [Effets des exercises physiques sur la cellularité adipeuse des femmes obèses préménopausées] *Cahiers Sante, 14*(3), 183-186.

64 Kraus, W. E., Houmard, J. A., Duscha, B. D., Knetzger, K. J., Wharton, M. B., & McCartney, J. S., et al. (2002). Effects of the amount and intensity of exercise on plasma lipoproteins.[see comment]. *New England Journal of Medicine, 347*(19), 1483-1492.

65 Heymsfield, S. B., Gallagher, D., Poehlman, E. T., Wolper, C., Nonas, K., & Nelson, D., et al. (1994). Menopausal changes in body composition and energy expenditure. *Experimental Gerontology, 29*(3-4), 377-389.

66 Lakka, T. A., & Laaksonen, D. E. (2007). Physical activity in prevention and treatment of the metabolic syndrome. *Applied Physiology, Nutrition and Metabolism, 32*(1), 76-88.

67 Carroll, S., Borkoles, E., & Polman, R. (2007). Short-term effects of a non-dieting lifestyle intervention program on weight management, fitness, metabolic risk, and psychological well-being in obese premenopausal females with the metabolic syndrome. *Applied Physiology, Nutrition and Metabolism, 32*(1), 125-142.

68 Gaspard, U., Buicu, C., & Creutz, V. (2001). Multiple benefits of physical exercise in menopausal women. [Multiples bénéfices de l'exercice physique chez la femme ménopausée.] *Revue medicale de Liege, 56*(4), 219-222.

69 Berlin, J. A., & Colditz, G. A. (1990). A meta-analysis of physical activity in the prevention of cardiovascular disease. *American Journal of Epidemiology, 132*(4), 612-628.

70 LaMonte, M. J., & Blair, S. N. (2006). Physical activity, cardiorespiratory fitness, and adiposity: Contributions to disease risk. *Current Opinion in Clinical Nutrition and Metabolic Care, 9*(5), 540-546.

71 Owens, J. F., Matthews, K. A., Wing, R. R., & Kuller, L. H. (1990). Physical activity and cardiovascular risk: A cross-sectional study of middle-aged premenopausal women. *Preventive Medicine, 19*(2), 147-157.

72 Kemmler, W., von Stengel, S., Weineck, J., Lauber, D., Kalender, W., & Engelke, K. (2005). Exercise effects on menopausal risk factors of early postmenopausal women: 3-yr erlangen fitness osteoporosis prevention study results. *Medicine & Science in Sports & Exercise, 37*(2), 194-203.

73 Lee, C. D., Folsom, A. R., & Blair, S. N. (2003). Physical activity and stroke risk: A meta-analysis.[see comment]. *Stroke, 34*(10), 2475-2481.

74 Conroy, M. B., Cook, N. R., Manson, J. E., Buring, J. E., & Lee, I. M. (2005). Past physical activity, current physical activity, and risk of cardiovascular disease. *Medicine & Science in Sports & Exercise, 37*(8), 1251-1256.

75 Warburton, D. E., Nicol, C. W., & Bredin, S. S. (2006). Health benefits of physical activity: The evidence. *CMAJ Canadian Medical Association Journal, 174*(6), 801-809.

76 Blair, S. N. (2003). Revisiting fitness and fatness as predictors of mortality. *Clinical Journal of Sport Medicine, 13*(5), 319-320.

77 Gerson, L. S., & Braun, B. (2006). Effect of high cardiorespiratory fitness and high body fat on insulin resistance. *Medicine and Science in Sports and Exercise, 38*(10), 1709-1715.

78 Hulens, M., Vansant, G., Lysens, R., Claessens, A. L., & Muls, E. (2001). Exercise capacity in lean versus obese women. *Scandinavian Journal of Medicine and Science in Sports, 11*(5), 305-309.

79 Carels, R. A., Darby, L. A., Cacciapaglia, H. M., & Douglass, O. M. (2004). Reducing cardiovascular risk factors in postmenopausal women through a lifestyle change intervention. *Journal of Women's Health (2002), 13*(4), 412-426.

80 Ross, R., Freeman, J., Hudson, R., & Janssen, I. (2002). Abdominal obesity, muscle composition, and insulin resistance in premenopausal women. *Journal of Clinical Endocrinology and Metabolism, 87*(11), 5044-5051.

81 Matsuzawa, Y., Funahashi, T. & Nakamura, T. (1999). Molecular mechanism of Metabolic Syndrome X: Contribution of adipocytokines·adipocyte-derived bioactive substances. *Annals of the New York Academy of Sciences,* 892, pp. 146-154.

82 Miyatake, N., Takanami, S., Kawasaki, Y., & Fujii, M. (2004). Relationship between visceral fat accumulation and physical fitness in japanese women. *Diabetes Research and Clinical Practice, 64*(3), 173-179.

83 Ross, R., & Katzmarzyk, P. T. (2003). Cardiorespiratory fitness is associated with diminished total and abdominal obesity independent of body mass index. *International Journal of Obesity, 27*(2), 204-210.

84 Lynch, N. A., Nicklas, B. J., Berman, D. M., Dennis, K. E., & Goldberg, A. P. (2001). Reductions in visceral fat during weight loss and walking are associated with improvements in Vo2 max. *Journal of Applied Physiology, 90*(1), 99-104.

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

86 Borodulin, K., Laatikainen, T., Lahti-Koski, M., Lakka, T. A., Laukkanen, R., & Sarna, S., et al. (2005). Associations between estimated aerobic fitness and cardiovascular risk factors in adults with different levels of abdominal obesity. *European Journal of Cardiovascular Prevention and Rehabilitation, 12*(2), 126-131.

87 Kemmler, W., Lauber, D., Weineck, J., Hensen, J., Kalender, W., & Engelke, K. (2004). Benefits of 2 years of intense exercise on bone density, physical fitness, and blood lipids in early postmenopausal osteopenic women: Results of the erlangen fitness osteoporosis prevention study (EFOPS). *Archives of Internal Medicine, 164*(10), 1084-1091.

88 Haddock, B. L., Hopp, H. P., Mason, J. J., Blix, G., & Blair, S. N. (1998). Cardiorespiratory fitness and cardiovascular disease risk factors in postmenopausal women. *Medicine and Science in Sports and Exercise, 30*(6), 893-898.

89 Boulé, N. G., Bouchard, C., & Tremblay, A. (2005). Physical fitness and the metabolic syndrome in adults from the quebec family study. *Canadian Journal of Applied Physiology, 30*(2), 140-156.

90 LaMonte, M. J., Barlow, C. E., Jurca, R., Kampert, J. B., Church, T. S., & Blair, S. N. (2005). Cardiorespiratory fitness is inversely associated with the incidence of metabolic syndrome: A prospective study of men and women. *Circulation, 112*(4), 505-512.

91 Lamonte, M. J., Ainsworth, B. E., & Durstine, J. L. (2005). Influence of cardiorespiratory fitness on the association between C-reactive protein and metabolic syndrome prevalence in racially diverse women. *Journal of Women's Health, 14*(3), 233-239.

92 Blair, S. N., & Jackson, A. S. (2001). Physical fitness and activity as separate heart disease risk factors: A meta-analysis. *Medicine and Science in Sports and Exercise, 33*(5), 762-764.

93 Carnethon, M. R., Gidding, S. S., Nehgme, R., Sidney, S., Jacobs, D. R.,Jr, & Liu, K. (2003). Cardiorespiratory fitness in young adulthood and the development of cardiovascular disease risk factors. *JAMA, 290*(23), 3092-3100.

94 Dvorak, R. V., Tchernof, A., Starling, R. D., Ades, P. A., DiPietro, L., & Poehlman, E. T. (2000). Respiratory fitness, free living physical activity, and cardiovascular disease risk in older individuals: A doubly labeled water study. *Journal of Clinical Endocrinology and Metabolism, 85*(3), 957-963.

95 Mercuro, G., Saiu, F., Deidda, M., Mercuro, S., Vitale, C., & Rosano, G. M. C. (2006). Impairment of physical exercise capacity in healthy postmenopausal women. *American Heart Journal, 151*(4), 923-927.

96 Lynch, N. A., Ryan, A. S., Berman, D. M., Sorkin, J. D., & Nicklas, B. J. (2002). Comparison of VO2max and disease risk factors between perimenopausal and postmenopausal women. *Menopause, 9*(6), 456-462.

97 Duncan, G. E., Li, S. M., & Zhou, X. H. (2005). Cardiovascular fitness among U.S. adults: NHANES 1999-2000 and 2001-2002. *Medicine & Science in Sports & Exercise, 37*(8), 1324-1328.

98 Pollock, M. L., Gaesser, G. A., Butcher, J. D., Després, J. -., Dishman, R. K., Franklin, B. A., et al. (1998). The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Medicine and Science in Sports and Exercise, 30*(6), 975-991.

99 Heyword, V. H. (2006). Assessing cardiorespiratory fitness. *Advanced fitness assessment and exercise prescription* (Fifth Edition ed., pp. 55). Champaign, IL: Human Kinetics.

100 MacArthur, D. G., & North, K. N. (2005). Genes and human elite athletic performance. *Human Genetics, 116*(5), 331-339.

101 Bouchard, C., Malina, R. M., & Perusse, L. (1997). In Enderle K. (Ed.), *Genetics of fitness and physical performance*. Champaign, IL: Human Kinetics.

102 Lakka, T. A., & Bouchard, C. (2004). Genetics, physical activity, fitness and health: What does the future hold? *Journal of the Royal Society for the Promotion of Health, 124*(1), 14-15.

103 Bouchard, C., An, P., Rice, T., Skinner, J. S., Wilmore, J. H., Gagnon, J., et al. (1999). Familial aggregation of VO(2max) response to exercise training: Results from the HERITAGE family study. *Journal of Applied Physiology, 87*(3), 1003-1008.

104 Prud'Homme, D., Bouchard, C., & Leblanc, C. (1984). Sensitivity of maximal aerobic power to training is genotype-dependent. *Medicine and Science in Sports and Exercise, 16*(5), 489-493.

105 Brindle, P., Beswick, A., Fahey, T., & Ebrahim, S. (2006). Accuracy and impact of risk assessment in the primary prevention of cardiovascular disease: A systematic review. *Heart, 92*(12), 1752-1759.

106 Katzmarzyk, P. T. (2007). The metabolic syndrome: An introduction. *Applied Physiology, Nutrition and Metabolism, 32*(1), 1-3.

107 Bentley-Lewis, R., Koruda, K., & Seely, E. W. (2007). The metabolic syndrome in women. *Nature Clinical Practice Endocrinology and Metabolism, 3*(10), 696-704.

108 Malik, S., Wong, N. D., Franklin, S. S., Kamath, T. V., L'Italien, G. J., Pio, J. R., et al. (2004). Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in united states adults. *Circulation, 110*(10), 1245-1250

109 Wannamethee, S. G., Shaper, A. G., Lennon, L., & Morris, R. W. (2005). Metabolic syndrome vs framingham risk score for prediction of coronary heart disease, stroke, and type 2 diabetes mellitus. *Archives of Internal Medicine, 165*(22), 2644-2650.

110 Noto, D., Barbagallo, C. M., Cefalù, A. B., Falletta, A., Sapienza, M., Cavera, G., et al. (2008). The metabolic syndrome predicts cardiovascular events in subjects with normal fasting glucose: Results of a 15 years follow-up in a mediterranean population. *Atherosclerosis, 197*(1), 147-153.

111 The Framingham Heart Study. (2002). *Estimating cardiovascular disease (CHD) risk using framingham heart study prediction score sheets* . Retrieved 12, 2006, from http://www.nhlbi.nih.gov/about/framingham/riskabs.htm

112 Pasternak, R. C., Abrams, J., Greenland, P., Smaha, L. A., Wilson, P. W., & Houston-Miller, N. (2003). 34th bethesda conference: Task force #1--identification of cardiovascular disease risk: Is there a detection gap? *Journal of the American College of Cardiology, 41*(11), 1863-1874.

113 Mieres, J. H., Shaw, L. J., Arai, A., Budoff, M. J., Flamm, S. D., Hundley, W. G., et al. (2005). Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: Consensus statement from the cardiac imaging committee, council on clinical cardiology, and the cardiovascular imaging and intervention committee, council on cardiovascular radiology and intervention, american heart association. *Circulation, 111*(5), 682-696.

114 Pilote, L., Dasgupta, K., Guru, V., Humphries, K. H., McGrath, J., Norris, C., et al. (2007). A comprehensive view of sex-specific issues related to cardiovascular disease. *CMAJ : Canadian Medical Association Journal = Journal De l'Association Medicale Canadienne, 176*(6), S1-44.

115 Peterson, P. N., Magid, D. J., Ross, C., Ho, P. M., Rumsfeld, J. S., Lauer, M. S., et al. (2008). Association of exercise capacity on treadmill with future cardiac events in patients referred for exercise testing. *Archives of Internal Medicine, 168*(2), 174-179.

116 Murtagh, J. (2003). The menopause and osteoporosis. ***General practice*** (Third ed., pp. 1008). Australia: McGraw-Hill Companies.

117 U.S. National Library of Medicine. (2005). *Medline plus, medical dictionary.* Retrieved 02, 2007, from http://www2.merriam-webster.com/cgi-bin/mwmednlm

118 U.S. National Library of Medicine. (2005). *Medline plus, medical dictionary.* Retrieved 11, 2006, from http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=Perimenopause

119 Svendsen, O. L., Hassager, C., & Christiansen, C. (1995). Age- and menopause-associated variations in body composition and fat distribution in healthy women as measured by dual-energy X-ray absorptiometry. *Metabolism: Clinical & Experimental, 44*(3), 369-373.

120 Torng, P. -., Su, T. -., Sung, F. C., Chien, K. -., Huang, S. -., Chow, S. -., et al. (2002). Effects of menopause on intraindividual changes in serum lipids, blood pressure, and body weight - the chin-shan community cardiovascular cohort study. *Atherosclerosis, 161*(2), 409-415.

121 Carr, M. C. (2003). The emergence of the metabolic syndrome with menopause. *Journal of Clinical Endocrinology and Metabolism, 88*(6), 2404-2411.

122 Brutsaert, T. D., Spielvogel, H., Caceres, E., Araoz, M., Chatterton, R. T., & Vitzthum, V. J. (2002). Effect of menstrual cycle phase on exercise performance of high-altitude native women at 3600 m. *Journal of Experimental Biology, 205*(2), 233-239

123 Constantini, N. W., Dubnov, G., & Lebrun, C. M. (2005). The menstrual cycle and sport performance. *Clinics in Sports Medicine, 24*(2), e51-e82.

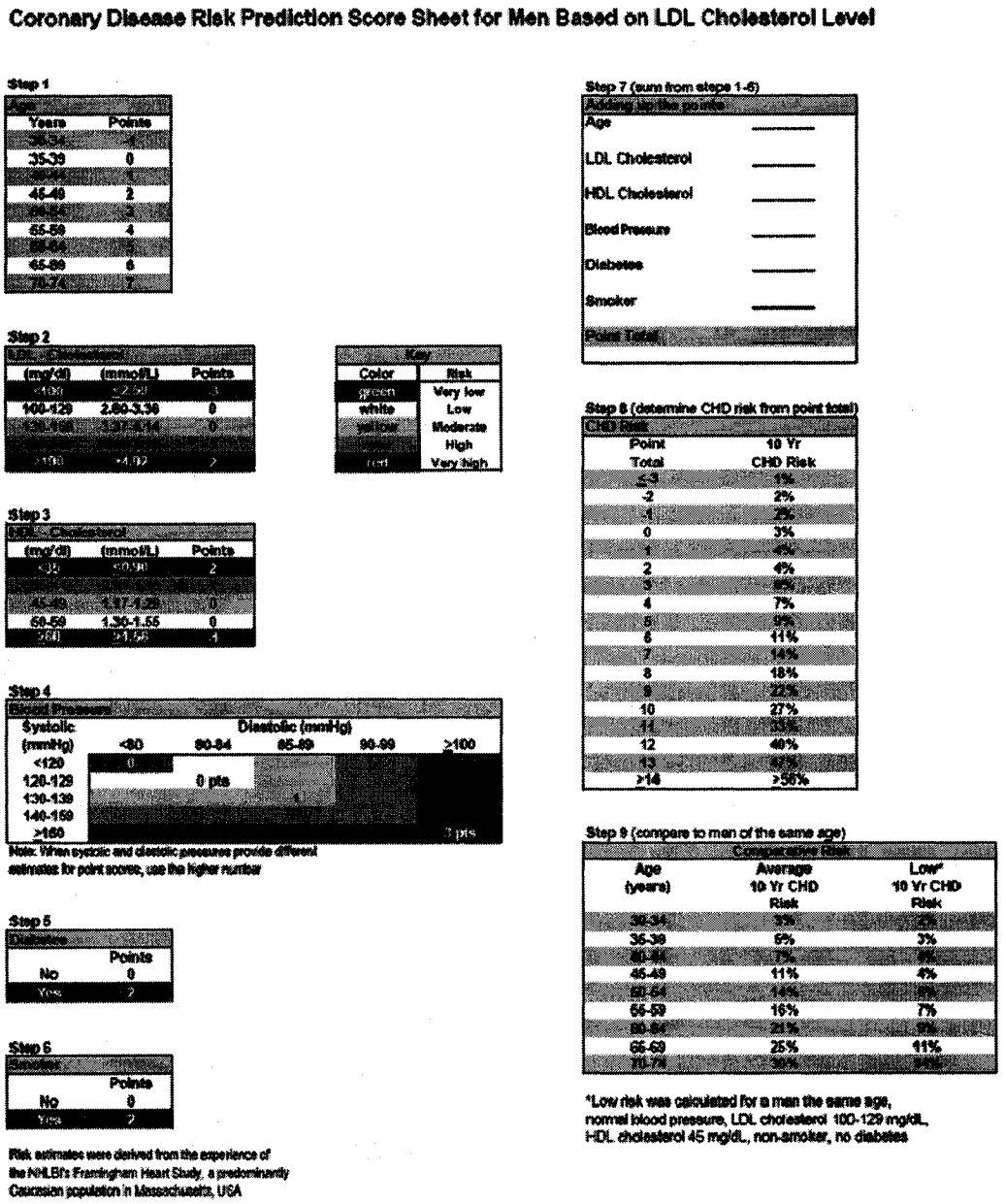
124 Giacomoni, M., Bernard, T., Gavarry, O., Altare, S., & Falgairette, G. (2000). Influence of the menstrual cycle phase and menstrual symptoms on maximal anaerobic performance. *Medicine and Science in Sports and Exercise, 32*(2), 486-492.

125 Smekal, G., Von Duvillard, S. P., Frigo, P., Tegelhofer, T., Pokan, R., Hofmann, P., et al. (2007). Menstrual cycle: No effect on exercise cardiorespiratory variables or blood lactate concentration. *Medicine and Science in Sports and Exercise, 39*(7), 1098-1106.

126 Yusuf, P.S., Hawken, S., Ôunpuu, S., Dans, T., Avezum, A., Lanas, F., McQueen, M., Budaj, A., Pais, P., Varigos, J. & Lisheng, L. (2004). Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): Case-control study. *Lancet,* 364(9438), 937-952.

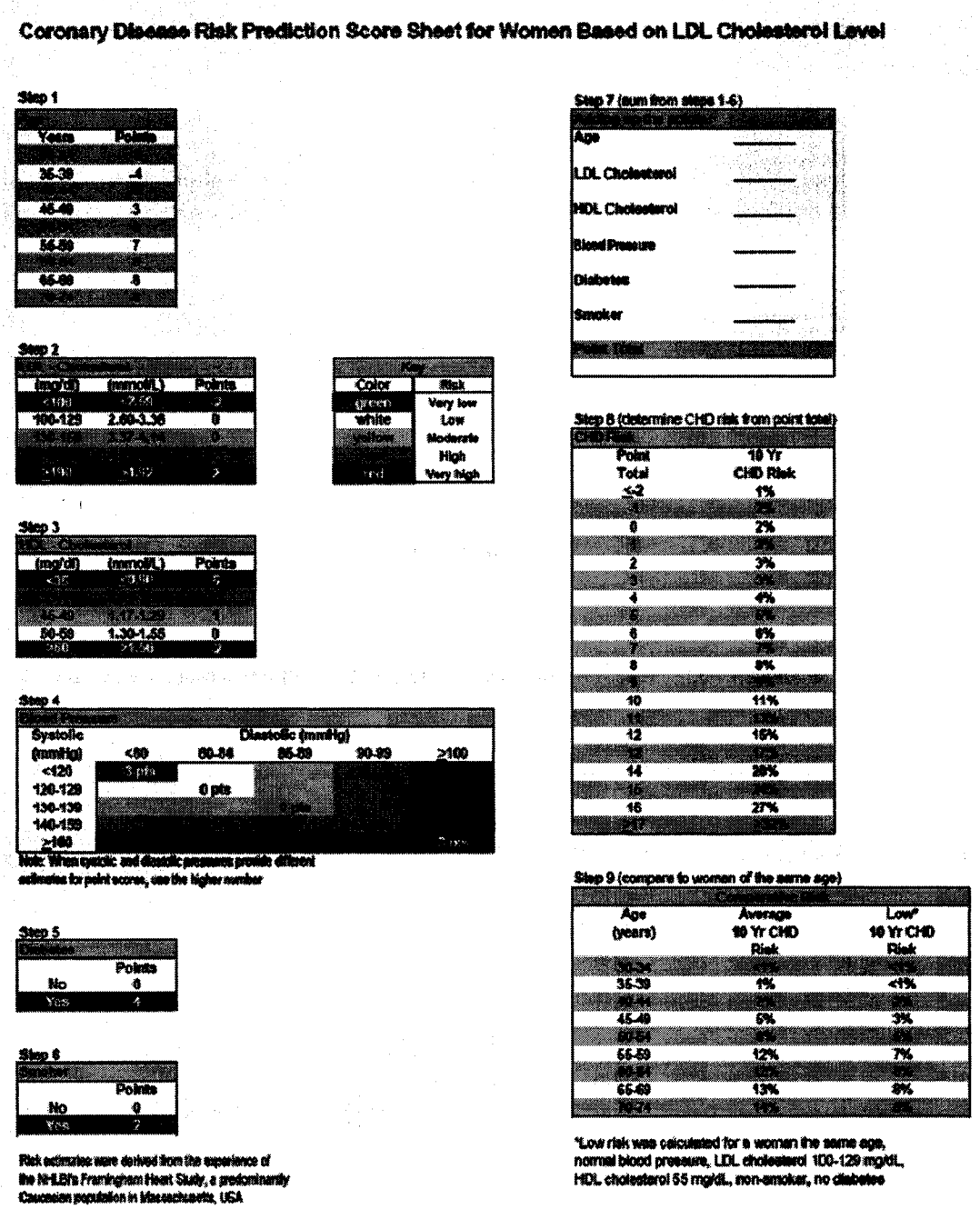
127 Sui, X., LaMonte, M.J., Laditka, J.N., Hardin, J.W., Chase, N., Hooker, S.P. & Blair, S.N. (2007). Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *Journal of the American Medical Association,* 298(21), 2507-2516.

APPENDIX A



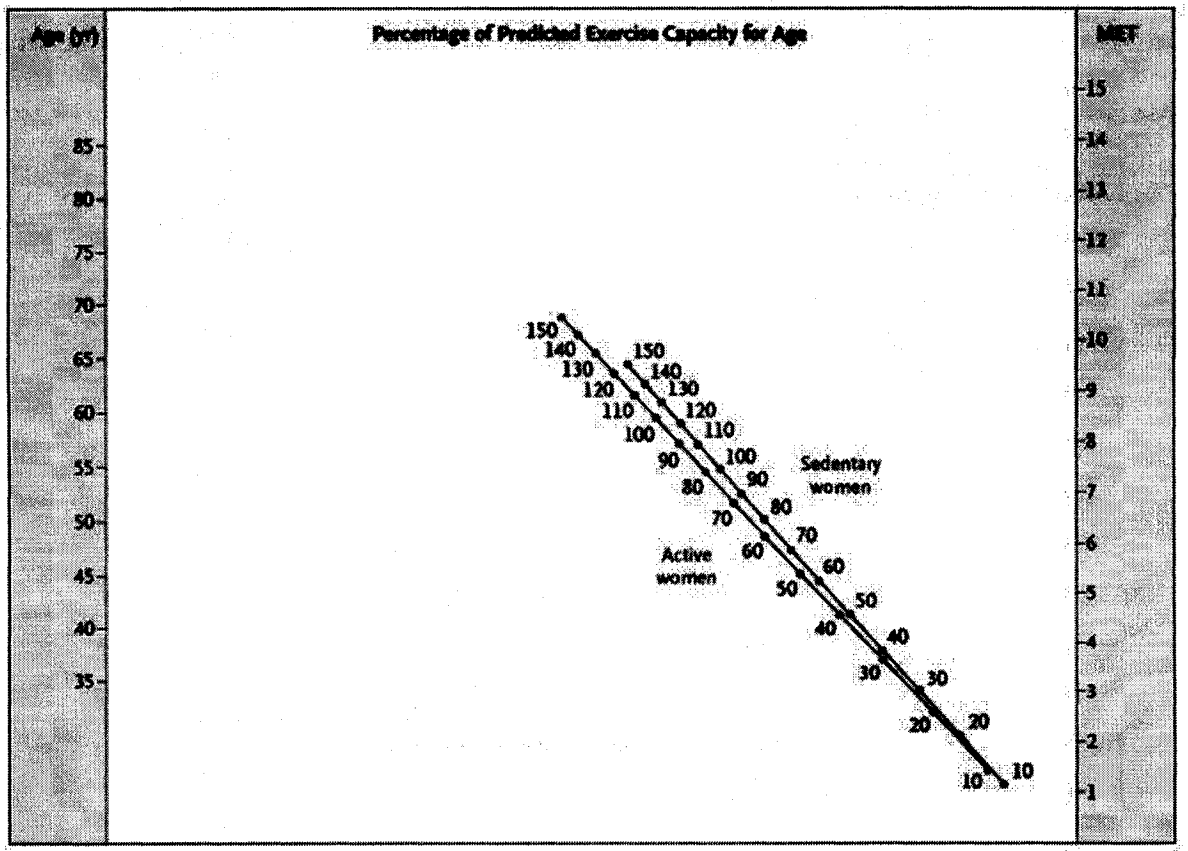
The Framingham Heart Study. (2002). ***Estimating cardiovascular disease (CHD) risk using framingham heart study prediction score sheets*** . Retrieved 12, 2006, from http://www.nhlbi.nih.gov/about/framingham/riskabs.htm

APPENDIX B



The Framingham Heart Study. (2002). ***Estimating cardiovascular disease (CHD) risk using framingham heart study prediction score sheets*** . Retrieved 12, 2006, from http://www.nhlbi.nih.gov/about/framingham/riskabs.htm

APPENDIX C



Nomogram of the Percentage of Predicted Exercise Capacity for Age (% PEC). % PEC = (MET observed / predicted MET for age) x 100. By drawing a straight line between the age and the exercise capacity will show the percentage of predicted exercise capacity for age. With permission (Appendix F)

Gulati, M., Black, H. R., Shaw, L. J., Arnsdorf, M. F., Merz, C. N., & Lauer, M. S., et al. (2005). The prognostic value of a nomogram for exercise capacity in women.[see comment]. *New England Journal of Medicine, 353*(5), 468-475.

APPENDIX D

BORG SCALE OF PERCEIVED EXERTION

6	
7	**Very, Very Light**
8	
9	**Very Light**
10	
11	**Fairly Light**
12	
13	**Somewhat Hard**
14	
15	**Hard**
16	
17	**Very Hard**
18	
19	**Very, Very Hard**
20	

Borg, G. A. V. (1982). Psychophysical bases of perceived exertion. *Medicine and Science in Sports and Exercise, 14*(5), 377-381.

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