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The relationship among inflammatory markers, physical fitness, and body mass index to cardiovascular disease

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THE RELATIONSHIP AMONG INFLAMMATORY MARKERS, PHYSICAL FITNESS, AND BODY MASS INDEX TO CARDIOVASCULAR DISEASE

By

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THE RELATIONSHIP AMONG INFLAMMATORY MARKERS.

PHYSICAL FITNESS, AND BODY MASS INDEX

TO CARDIOVASCULAR DISEASE

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10,291 participants, aged 20 to 85 years of age, available from the 1999 through 2002 NHANES databases participated in this study. Only 8,485 (82%) participants were included in the data analysis, which was collected at Mobile Examination Centers (MEC). Participant's who were pregnant (n = 603), not examined at MEC (n = 820), or had missing values for height (n = 164) and/or weight (n = 125) were eliminated. Individuals were classified into four groups (underweight, normal, overweight and obese) based on body mass index (BMI). Variables measured in the study included body mass index, physical fitness, dietary folic acid, c-reactive protein, homocysteine, folate, serum total cholesterol, serum triglycerides, HDL-C, and glucose. The results of this study showed being overweight and obese were associated with poor serum lipid profile, higher

serum glucose levels, lower participation in physical activity, lower physical fitness level, and higher serum levels of inflammatory markers for cardiovascular disease (CVD).

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CHAPTER I

INTRODUCTION

Cardiovascular disease (CVD) is a broad term referring to numerous conditions characterized by dysfunction of the heart and blood vessels. One in four Americans, over 60 million persons, will experience some type of CVD during their lifetime. CVD is the leading cause of death in the United States, accounting for approximately 910,000 deaths per year. Many factors are linked to the development of CVD, including blood cholesterol levels, hypertension, physical inactivity, diet and cigarette smoking (Center for Disease Control and Prevention, 2006). These factors influence the development of the two major forms of CVD, which are termed atherosclerosis and arteriosclerosis. Atherosclerosis is an accumulation of plaque that causes narrowing for the blood vessel and an eventual loss of blood vessel elasticity (Gylys & Wedding, 2005). Arteriosclerosis is a hardening of the arterial walls that usually results from an accumulation of a plaque-like substance composed of cholesterol, lipids and cellular debris along the innermost lining of the arterial walls (Gylys & Wedding, 2005).

Development of atherosclerosis and arteriosclerosis occurs over a long period of time (Scott, 2004). Three common manifestations of CVD related to atherosclerosis and

arteriosclerosis are heart attack or myocardial infarction, heart failure, and stroke (Scott, 2004). Ischemic heart disease, coronary heart disease (CHD), or coronary artery disease (CAD) all refer to the same condition that results from accumulation of plaque within the coronary blood vessels, and accounts for the approximately 35% of all deaths in United States annually. Deaths may occur suddenly as a result of an acute coronary artery occlusion (ischemic heart disease) or cardiac fibrillation (Scott, 2004).

Research shows that factors such as physical activity, diet, body mass index (BMI), and inflammatory markers are linked to CVD. Many studies have demonstrated that physical activity has a great impact on health and mortality. Results from many studies, including the Harvard Alumni Health Study (Lee, Hsieh, & Paffenbarger , 1995), British Civil Service Study (Morris et al., 1980), Multiple Risk Factor Intervention Trial (Leon et al., 1997) and Caerphilly Study (Yu, Yarnell, Sweetman, & Murray, 2003), demonstrated that physical activity reduces risk of all-cause mortality, CVD, and mortality related to CVD. More recently, studies have focused on the intensity as well as the amount of physical activity required to obtain a reduction in CVD risk (Yu et al., 2003). Aerobic exercise of high intensity clearly has been demonstrated to reduce CVD incidence and CVD-related mortality (Yu et al., 2003). Some, but not all, studies show that participation in exercise of moderate intensity also decreases the occurrence of CVD and CVD-related mortality (Barengo, Hu, Lakka, Pakkarinen, Nissinen, & Tuomilehto, 2004; Leon, Myers, & Connett, 1997). The United States Dietary Association's Dietary Guidelines recommend participation in physical activity at a level that matches the number of calories expended with calories consumed, and walking or doing other

physical activity of a minimum of 30 minutes per day on most days of the week (American Heart Association, 2006). Current American College of Sports Medicine guidelines recommend that individuals participate in a minimum of 30 minutes or more of moderate intensity physical activity on three or more days per week in order to acquire the beneficial effects of exercise (Anderson, Blair, Cheskin, & Bartlett, 1997); (American College of Sports Medicine, 1998).

Participation in physical activity programs typically increases cardiorespiratory fitness, which is often assessed using maximal oxygen consumption (VO_2max). Individuals with higher levels of cardiorespiratory fitness have reduced risks of progression of CAD and death due to CVD compared with individuals with low fitness (Lakka, Laukkanen, Rauramaa, Salonen, Lakka, Kaplan et al., 2001; Laukkanen, Lakka, Rauramaa, Kuhanen, Venalainene, Salonen, et al., 2001).

Although physical activity plays a significant role in reducing CVD risk, BMI also contributes to the risk for CVD. BMI is a measure of an individual's body weight relative to height, and is expressed as kilograms of body weight per height in square meters. In general, a greater BMI is associated with an increase in body fatness. In the United States, over 60% of individuals are overweight based on BMI ($BMI \geq 25\ kg/m^2$), and approximately 25% of the population is obese ($BMI \geq 30\ kg/m^2$) (Center for Disease Control and Prevention, 2003). The Framingham Heart Study demonstrated that risk for CVD was increased in overweight and obese men and women compared to men and women of normal weight (Wilson, Garrison, Castelli, Feinleib, McNamara, Kannel et al., 1980). In the Caerphilly Prospective Study, men with BMI values of $30\ kg/m^2$ or greater

were at increased risk for CHD and overall mortality (Yarnell, Patternson, Hugh, & Sweetman, 2000). In the Whitehall study of London-based male government employees there was an elevated risk of mortality related to CHD in overweight and obese men (Batty, Shipley, Jarrett, Breeze, Marmot & Davey Smith., 2005).

Many studies have established a link between serum cholesterol and CVD. Serum cholesterol is a strong predictor of CHD and all-cause mortality in middle-aged populations (Anderson, Castelli, & Levy, 1987; Benfante & Reed, 1990; Martin, Hulley, Browner, Kuller, & Wentworth., 1986). Increased levels of low-density lipoprotein-cholesterol (LDL-C) have been associated with the progression of CVD (Huxley, Lewington, & Clarke, 2002; Nicholls & Lundman, 2004), while greater levels of HDL are inversely related to CVD. It is very important to note that conventional markers for CVD risk do not accurately predict the likelihood of CVD in many individuals (Blake & Ridker, 2002). Inflammatory markers, especially C-reactive protein (CRP) and homocysteine, may have stronger relationships than cholesterol levels with progression of coronary artery disease (Rasouli, Nasir, Blumenthal, Park, Aziz, & Budoff, 2005).

Overweight and obesity may affect the heart and cardiovascular system through its influence on many risk factors, such as dyslipidemia, glucose intolerance, inflammatory markers, hypertension and promotion of a prothrombotic state (Poirier & Despres., 2006). Overweight and obesity predispose to or are associated with numerous cardiac complications such as coronary heart disease, heart failure, and sudden death because of their impact on the cardiovascular system. Higher blood glucose levels are a marker for impaired glucose tolerance or increased resistance to insulin. Elevated blood

glucose has been linked to an increased risk of CVD (Bowman & Armitage, 2002: Petersen & McGuire, 2005; Schnell, 2005). Furthermore, elevated serum glucose levels have been linked with low grade inflammation (Barzilay & Freedland, 2003). Reduction in body weight, especially body fatness, and participation in physical activity may improve blood glucose levels, thus decreasing the likelihood of CVD.

Inflammatory mechanisms play a prominent role in mediating all stages of atherosclerosis, and measurement of inflammatory biomarkers, such as CRP, may be useful for detecting individuals at risk for CVD. CRP is present at very low levels in the blood and is an extremely sensitive marker of inflammation. CRP may originate from various tissues, which apparently includes plaque formed through the atherosclerotic process (Blake & Ridker, 2002). Evidence from observational studies indicates that CRP is the strongest predictor of future myocardial infarction and stroke (Koenig, 2005; LaMonte, Durstine, Yanowitz, Lim, DuBose, Davis, et al 2002). In fact, CRP has been shown to accurately predict risk of cardiovascular events even in individuals with low levels of LDL-C (Nambi & Balantyne, 2005). The addition of CRP to standard lipid screening may improve global risk prediction among those with high as well as low cholesterol levels.

Results of studies examining the effect of regular physical activity on CRP levels are somewhat equivocal. Cross-sectional studies suggest that physical activity reduces CRP levels (Colbert, Visser, Simonsick, Tracy, Newman, Kritchevsky et al., 2004; Reuben, Judd-Hamilton, Harris, & Seemanet, 2003), but results from longitudinal studies are inconsistent (Lakka, Lakka, Rankinen, Leon, Rao, Skinner.et al., 2005; Nicklas et al.,

2004; Rauramaa, Halonen, Vaisanen, Lakka, Schmidt-Trucksass, Berg et al., 2004). BMI and body fatness appear to be more closely associated with CRP levels than physical activity (Tamakoshi, Yatsuya, Kondo, Ishikawa, Zhang, Murata et al., 2003; Thorand, Baumert, Doring, Herder, Kolb, Rathmann, et al., 2006), and reductions in body weight and fatness result in declines in CRP (Tchernof, Nolan, & Sites, 2002).

Homocysteine is another prominent inflammatory marker that has been shown to be related significantly to CVD risk (Aronow & Ahn, 2000; Kario, Duell, Matsuo, Sakata, Kato, Shimada et al., 2001; Lindeman, Romero, Yau, Koehler, Baumgartner, & Garry, 2003; Nurk, Tell, Vollset, Nygard, Refsum, & Ueland, 2002). Homocysteine can induce damage of the tunica intima of the arterial wall and trigger atherosclerosis. Most, but not all, observational epidemiological studies indicate that individuals with higher homocysteine levels have increased risks of CVD. The magnitude ranges from approximately 20% in prospective studies to approximately 80% in retrospective case-control studies (Splaver, Lamas, & Hennekens, 2004). Homocysteine levels are related to physical activity, BMI, diet and other lifestyle factors. Individuals who are physically active are more likely to have lower homocysteine levels (Dankner, Chetrit, Lubin, & Sela, 2004; Panagiotakos, Pitsavos, Zeimbekis, Chryysohoou, & Stefanadis, 2005). Homocysteine levels were positively related with BMI in young and older women (Rasmussen Ovesen, Bulow, Knudsen, Laurberg, & Perrild, 2000), as well as in obese children and adolescents (Gallistl, Sudi, Erwa, Aigner, & Borkenstein, 2001). Homocysteine has been shown to be inversely related to dietary folate (Coombes, Fraser, Sharman, & Booth, 2004) and serum folate (Lindemann et al., 2003). Physical activity

and a reduction in body fatness may improve homocysteine levels, thus decreasing the risk of CVD (Colbert et al., 2004).

Physical activity increases physical fitness and plays a major role in the reduction of many diseases including CVD. Physical activity also may assist with maintenance of a healthy body weight. Blood lipid levels as well as the inflammatory markers, CRP and homocysteine, are related to CVD incidence. Exercise decreases the occurrence of CVD if performed on a consistent basis, but there is a lack of research on the effect of physical activity on CRP and homocysteine (Anderson et al, 1997). The purpose of this study was to determine the relationship between BMI and physical fitness, blood lipids, and inflammatory markers, as well as the relationship of these variables to cardiovascular disease using data from the National Health and Nutrition Examination Survey (NHANES) 1999 - 2002. It was hypothesized that 1) individuals who were normal weight based on BMI classification would have higher levels of physical fitness compared to overweight and obese individuals; 2) individuals who were normal weight would have lower serum triglyceride and total cholesterol levels compared with overweight and obese individuals; 3) individuals who were normal weight would have lower serum glucose levels compared with overweight and obese individuals; 4) individuals who were normal weight would have lower serum levels of the inflammatory markers, CRP and homocysteine, for CVD compared with overweight and obese individuals; and, 5) individuals who were normal weight would have a greater age when they were told that they had CHD compared with overweight and obese individuals.

CHAPTER II

LITERATURE REVIEW

Introduction

Cardiovascular disease (CVD) is a broad term referring to numerous abnormal conditions that are characterized by dysfunction of the myocardium and blood vessels. CVD includes arteriosclerosis and atherosclerosis and is the leading cause of death in the United States, accounting for approximately 910,000 deaths per year (Center for Disease Control and Prevention, 2006). Arteriosclerosis is a hardening of the arterial walls that usually results from an accumulation of a plaque like substance composed of cholesterol, lipids and cellular debris. This plaque accumulates on the tunica intima or innermost lining of the arterial walls. Atherosclerosis is primarily a disease of the large arteries in which lipid deposits referred to as atheromatous plaques appear on the inside layers of the arteries (Gylys & Wedding, 2005). These plaques contain large amounts of cholesterol and are associated with degeneration of the arterial walls. In later stages of the disease, fibroblasts infiltrate the degenerative areas and cause progressive sclerosis of the arteries. The plaques often extend through the intima of the blood vessel wall, protruding into the

blood vessels and blocking blood flow. Additionally, calcium often precipitates with the lipids to develop calcified plaques, resulting in a loss of elasticity or "hardening" of the arteries. The loss of elasticity causes the atherosclerotic arteries to rupture more readily. Finally, the roughened internal surface of the arteries can induce localized hemorrhage of blood into the plaque that forms a clot or thrombus. A thrombus can cause an acute obstruction of blood flow through the arteries resulting in partial or complete disruption of blood flow to the myocardium or other tissues. Also, thrombi can dislodge and move through the circulation as emboli. An embolus, which is defined as a mass of undissolved matter circulating in the blood, can lodge in a blood vessel causing a localized infarct (Gylys & Wedding, 2005).

Ischemic heart disease, coronary heart disease (CHD), or coronary artery disease (CAD) all refer to the same condition and result from accumulation of plaque within the coronary blood vessels. Approximately 20% of the total cardiac output is necessary to meet the oxygen demands of the cardiac muscle. When blood flows through the coronary arteries to localized areas of the myocardium is decreased, ischemia or lack of adequate oxygenation occurs that can cause pain or angina pectoris. A complete lack of oxygen results in a myocardial infarction and necrosis of the affected tissue. CHD accounts for approximately 35% of all deaths in the United States.

There are numerous risk factors for CVD, some of which are genetically determined and cannot be modified while other risk factors are modifiable. Risk factors that can be modified include physical activity level, diet, and smoking. Increasing physical activity is associated with a reduction in the risk for CHD; however, more than

60% of adults in the United States are not physically active on a regular basis and 25% do not participate in any physical activity (US Department of Health and Human Services). Studies have demonstrated that higher levels of regular physical activity (Anderson, et al. 1997, Leon et al., 1987) and cardiorespiratory fitness (Lakka, Venalainen, Rauramaa, Salonen, Tuomilehto, & Salonen, 1994) are associated with a reduced risk of CVD.

The Relationship of Physical Activity and Physical Fitness with Mortality and Cardiovascular Disease

It is widely accepted that regular physical activity is associated with a reduced risk of many chronic diseases, including CVD. Classic epidemiological studies have established that increasing levels of physical activity are inversely associated with the risk of CVD (Leon, Myers, & Connett, 1997; Morris, Everit, Pollard, Chave, & Semmence, 1980; Paffenbarger, Hyde, Wing, Lee, Jung, Kampert, 1993; Rosengren & Wilhelmsen, 1997). More recent studies have focused on the quantity and intensity of physical activity necessary to reduce the risk for CVD. While the benefits of physical activity of high or vigorous intensity are clear (Yu et al., 2003), the benefits of light and moderate intensity exercise are equivocal (Barengo et al., 2004; Yu et al., 2003).

Results of the Harvard Alumni Health Study showed an inverse relationship between physical activity and all-cause mortality and CVD mortality in men (Lee et al., 1995). In the Harvard Alumni Health Study, 12,516 middle-aged and older men (mean age of 57.7 years) were followed from 1977 through 1993. Sports or recreational activities were reported by 74.1% of the men. Compared with men expending fewer than 2,100 kilojoules (kJ) per week, men expending 4,200 to 8,400 kJ per week had a 20%

reduction in risk for CHD (Sesso, Paffenbarger, & Lee, 2000). Expending over 8,400 kJ per week did not result in further reduction in CHD risk. Among men with multiple coronary risk factors, those expending greater than 4,200 kJ per week had reduced CHD risk compared with men expending less than 4,200 kJ per week. Most of the energy was expended during moderate (4 to < 6 multiples of the resting metabolic equivalent (METs)) and vigorous (≥ 6 METs) activities. Only total sports or recreational activities and vigorous activities were associated with a decreased risk of CHD; light and moderate activities were not associated with a reduction in risk for CHD. The authors expressed concern that activities of light and moderate intensity may not have been measured precisely (Sesso et al., 2000).

In another part of the Framingham study, the relationships of lifestyle changes to all-cause mortality and death from CHD were examined in men who were 45 to 84 years of age in 1977 and who had reported no life-threatening disease on questionnaires completed in 1962 or 1966 and again in 1977 (Paffenbarger et al., 1993). Men were classified according to lifestyle changes between completion of the first and second questionnaires. Men who initiated participation in sports of moderately vigorous intensity, defined as great than 4½ METs, had a 23% lower risk of death from CHD compared with men who did not take up moderately vigorous exercise (Paffenbarger et al. 1993).

The relationship between physical activity and the incidence of CHD was studied in 17,944 middle-aged male British Civil Service office workers (Morris et al., 1980). Men who reported engaging in vigorous sports during an initial survey in 1968-70 had an

incidence of CHD over the following 8½ years that was approximately half that of their colleagues who reported no vigorous exercise (Morris et al., 1980). Fatal and non-fatal clinical events related to CHD were lower for men reporting participation in vigorous exercise. This benefit of vigorous exercise was notable in individuals across all age-ranges studied, but was more striking in individuals of later-middle age and early-old age. Vigorous exercise also reduced non-fatal and fatal clinical events in all of the other sub-groups examined, including men with a family history of CHD, men with severe hypertension and sub-clinical angina, obese men and cigarette smokers (Morris et al., 1980).

Data from the Multiple Risk Factor Intervention Trial (MRFIT), a prospective study of 12,138 middle-aged men at high risk for CHD, showed that a relatively small amount of daily moderate intensity leisure time physical activity (LTPA) can reduce CHD-related mortality (Leon et al., 1997). Men were classified into deciles based on average minutes per day (min/d) of LTPA reported at baseline, which was compared with cumulative CHD and all-cause mortality after 16-years of follow-up. Men in the least-active decile for LTPA, who averaged 4.9 min/d of LTPA, had excess age-adjusted mortality rates of 29% and 22% for CHD and all-causes, respectively, as compared to those in combined deciles 2 to 4, who averaged 22.7 min/d of predominantly light and moderate LTPA. No further decrement in mortality rates was noted in those in the higher deciles of LTPA. The MRFIT demonstrates that a modest amount (10 to 36 min/d) of moderate intensity LTPA can significantly reduce premature mortality, particularly from CHD, in middle-aged and older men at high risk for CHD (Leon et al., 1997). Data from

MRFIT published after seven years of follow-up showed that moderate LTPA was associated with 63% fewer fatal CHD events and sudden deaths and 70% fewer total deaths compared with low LTPA (Leon et al., 1987). Combined fatal and nonfatal major CHD events were 20% lower with high LTPA as compared with low LTPA. It was concluded that LTPA has a modest inverse relation to CHD and overall mortality in middle-aged men at high risk for CHD (Leon et al., 1987).

The relationship between LTPA and CHD disease mortality and all-cause mortality was examined in white male US railroad workers during 17 to 20 years of follow-up (Slattery, Jacobs, & Nichaman, 1989). The cohort, which was initially examined from 1957 to 1960 and reexamined from 1962 to 1964, was followed until either 1977 or death. The risk estimate for death from CHD, after adjusting for age, was 1.39 for sedentary men who expended 40 kilocalories (kcal) per week in LTPA compared with very active men who expended 3,632 kcal per week. Although the risk estimate was mitigated when adjusted for other CHD risk factors it remained statistically significant. Caloric expenditure from light and moderate activity, as well as that performed during intense activity, showed independent relationships to cardiovascular death and all-cause mortality. The US railroad workers' study demonstrated that physical activity reduces all-cause mortality and mortality due to CHD (Slattery et al., 1989).

The relationship of moderate or high LTPA or occupational physical activity and commuting activity with all-cause mortality and CVD-related mortality were studied as part of a prospective follow-up (median follow-up time 20 years) of 15,853 men and 16,824 women, aged 30 to 59 years, living in eastern and south-western Finland (Barengo

et al., 2004). CVD and all-cause mortality were reduced 9 to 21% in men and 2 to 17% in women who were moderately or highly physically active during leisure time. Moderate and high levels of occupational physical activity also reduced CVD-related and all-cause mortality by 21 to 27% in men and women. Women who spent at least 15 minutes per day walking or cycling to and from work had a reduced CVD-related and all-cause mortality prior to adjusting for occupational and LTPA. Commuting activity was not associated with CVD-related or all-cause mortality in men. Moderate and high levels of LTPA and occupational physical activity are associated with a reduced CVD and all-cause mortality in both men and women (Barengo et al., 2004).

In an observational study of 9,824 U.S. adults, aged 51 to 61 years in 1992, individuals who performed regular moderate to vigorous physical activity had a substantially lower overall mortality, odds ratio = 0.62, compared with sedentary individuals (Richardson, Kriska, Lantz, & Hayward, 2004). Participants performing regular moderate to vigorous exercisers had an odds ratio of 0.55 for CVD related mortality compared to sedentary individuals. Even persons performing occasional or light exercises had an odds ratio of 0.55 compared with sedentary individuals. Individuals with the greatest CVD risk had the most significant benefit from being physically active (Richardson et al., 2004).

In a 16-year follow-up study of middle-aged men and women in Finland, an increase in self-reported LTPA appeared to have similar beneficial effect on the mortality risk of obese and nonobese men and women, as well as for fit and unfit subjects (Haapanen-Niemi, Miilunpalo, Pasanen, Vuori, Oja, et al., 2000). There was a very

strong relationship between LTPA and CVD in women with a relative risk of 4.68 for women reporting no vigorous physical activity compared with the most active women. In men, the relationship was weaker, with a relative risk for CVD of 1.61 for men reporting no LTPA compared with the most active men (Haapanen-Niemi et al., 2000).

The Whitehall study was a prospective cohort study of London civil servants that followed 6,702 men, aged 40 to 64 years at entry into the study, for up to 25 years (Davey Smith, Shipley, Batty, Morris, & Marmot, 2000). LTPA was inversely associated with mortality from all-causes, CHD, and other types of CVD following adjustment for other risk factors. Walking pace was inversely associated with all-cause mortality, as well as mortality from CHD and other CVD (Davey Smith et al., 2000).

Although there is debate about the importance of physical activity compared with physical fitness in relation to risk for CVD, participation in physical activity programs typically increases cardiorespiratory fitness. The most important measurement of cardiorespiratory fitness is maximal oxygen consumption (VO_2max). The Kuopio Ischemic Heart Disease Risk Factor Study, a population-based cohort study of 1,294 healthy men in Kuopio and surrounding communities in eastern Finland, examined the relationship of cardiorespiratory fitness at the initiation of the study with overall- and CVD-related mortality (Laukkanen et al., 2001). Maximal oxygen consumption and exercise duration during a fitness test were measured in order to assess cardiorespiratory fitness. The men were followed for an average time of 10.7 years. There was a higher mortality rate in unfit men compared to fit men. The relative risk of death due to all causes was 2.76 unfit men (VO_2max < 27.6 milliliters per kilogram per minute (ml/kg

per minute)) compared to fit men (VO_2max > 37.1 ml/kg per minute) after adjusting for age, examination years, smoking, and alcohol consumption. The relative risk for death due to CVD was 3.09 in unfit compared to fit men. Additional adjustments for various factors including serum lipid levels, blood pressure, plasma fibrinogen level, diabetes, and fasting serum insulin level did not alter these associations significantly. Also, duration of the exercise test had a strong inverse relationship with overall and CVD-related mortality. It was concluded that both maximal oxygen uptake and the duration of the exercise test were strong predictors of all-cause mortality as well as CVD-related mortality (Laukkanen et al., 2001).

Over an average follow-up of 4.9 years in 1,453 men, 42 to 60 years of age upon entry into the study, the relative risk of myocardial infarction in the upper third of subjects with the highest level of physical activity (> 2.2 hours physical activity per week) was 0.31 as compared with subjects in the lower third for physical activity level (Lakka et al., 1994). The relative risk of myocardial infarction for study participants in the upper third for maximal oxygen uptake (> 2.7 liters per minute) was 0.26 after adjustment for age and other factors. Even after adjustment for up to 17 confounding variables, there was little change in relative risk for subjects in the highest third for physical activity or maximal oxygen uptake as compared with the participants in the lowest third. Higher levels of both LTPA and cardiorespiratory fitness had strong, graded, inverse relationships with the risk of acute myocardial infarction, supporting the hypothesis that lower levels of physical activity and cardiorespiratory fitness are independent risk factors for CHD (Lakka et al., 1994).

The relationship between cardiorespiratory fitness and the progression of early carotid atherosclerosis was examined during a 4-year follow-up study in men, 42 to 60 years of age. VO_2max, which is a measure of cardiorespiratory fitness, had strong, inverse, and graded associations with 4-year increases in progression of carotid atherosclerosis (Lakka et al., 2001). Good cardiorespiratory fitness was shown to be associated with slower progression of early atherosclerosis in middle-aged men (Lakka et al., 2001).

The Relationship of the Duration and Intensity of Physical Activity with Mortality and Cardiovascular Disease

It is unclear whether the total amount of physical activity, often expressed as total energy expended, or the intensity of physical activity, which is represented as the rate of energy expenditure, is more important in reducing CVD or CHD risk. Some studies demonstrate that regular, vigorous physical activity is necessary for a decreased risk of CVD and CHD-related mortality (Morris et al., 1980; Laaka et al. 1994). Other studies show that the total amount of energy expenditure, including that of moderate intensity, is sufficient to decrease the CVD and CHD-related mortality (Leon et al., 1987; Paffenbarger et al., 1993; Slattery et al., 1989). The United States railroad workers study showed that both moderate and vigorous activity could contribute to the reduction in CVD-related death (Slattery et al., 1989).

Data from the Framingham Heart Study demonstrated that the duration of physical activity played a key role in extending life expectancy and the number of years lived without CVD (Franco, Peeters, Bonneux, & De Laet, 2005). Data were used to

calculate the consequences of three different physical activity levels (low, moderate, and high) after age 50 years on total life expectancy and life expectancy with and without CVD. Hazard ratios for three transitions (healthy to death, healthy to disease, and disease to death) were calculated by levels of physical activity and adjusted for age, sex, smoking status and co-morbidities. In men, moderate and high levels of physical activity levels were associated with a calculated increase in life expectancy of 1.3 and 3.7 years, respectively. Also, moderate and high levels of physical activity levels increased the amount of time lived without CVD by 1.1 and 3.2 years, respectively compared with those who maintained a low physical activity level. For women, moderate and high levels of physical activity levels increased life expectancy 1.5 and 3.5 years, respectively, and also increased the amount of time lived free of CVD by 1.3 and 3.3, respectively. Engaging in moderate or high levels of physical activity not only increases life expectancy, but also extends the CVD-free life expectancy in both men and women (Franco et al., 2005).

The relationship between the duration and intensity of LTPA and the risk of CHD was examined in healthy middle-aged men and women, aged 35 to 63 years, in northeastern Finland during 10 years of follow-up (Haapanen, Miilunpalo, Pasanen, Oja, & Vuori, 1997). Subjects were divided into groups based on the amount of LTPA (three levels) and the intensity of LTPA (two levels). An increase in the total amount of LTPA was associated with a reduced CHD risk in men but not among women. After adjustment for smoking status, the risk of CHD in men was twice as great in the low duration LTPA group compared with the high duration LTPA group (Haapanen et al, 1997). The

intensity of LTPA was not statistically associated with the risk of CHD for either men or women (Haapanen et al., 1997).

A cohort of 44,452 men, who were enrolled in the Health Professionals' Follow-up Study, were followed at 2-year intervals for 12 years (Tanasescu, Leitzmann, Rimm, Willett, Stampfer, & Hu, 2003). Total physical activity, running, weight training, and rowing were each inversely associated with risk of CHD. Men in the two highest quintiles of total physical activity had a reduced relative risk for incident nonfatal myocardial infarction or fatal CHD occurring during the follow-up period compared to men in the lowest physical activity quintile. Men who ran for an hour or more per week had a 42% risk reduction compared with men who did not run. Men who performed resistance training for 30 minutes or more per week had a 23% risk reduction compared with men who did not train with weights. Rowing for one hour or more per week was associated with an 18% risk reduction. Average exercise intensity was associated with reduced CHD risk independent of the total volume of physical activity. Participants engaging in physical activity corresponding to high intensities (6 to 12 METs) had a decreased relative risk for incident nonfatal myocardial infarction or fatal CHD compared with individuals who performed on low intensity activity (< 4 METs) (Tanasescu et al., 2003). Individuals participating in moderate intensity activity (4 to 6 METs) did not have a significant reduction in risk. One-half hour per day or more of brisk walking was associated with an 18% risk reduction. and walking pace was associated with reduced CHD risk independent of the number of walking hours. Total physical activity, running, weight training, and walking were each associated with reduced CHD risk. Average

exercise intensity was associated with reduced risk independent of the number of MET-hours spent in physical activity (Tanasescu et al., 2003).

The Caerphilly study examined the optimal intensity of LTPA that was associated with a decreased risk of all-cause mortality, as well as mortality due to CVD and CHD, in middle-aged British men during 11 years of follow-up (Yu et al., 2003). Cumulative LTPA had a significant and graded relationship with all-cause, CVD and CHD mortality. When different intensities of activity were considered, light and moderate intensity LTPA had inconsistent and non-significant relations with all-cause, CVD, or CHD mortality whether adjusted only for age or adjusted for other cardiovascular risk factors as well. In contrast, there was a significant dose-response relationship between heavy intensity LTPA for all-cause, CVD, and CHD mortality even after adjustment for other risk factors. In a population of men without evidence of CHD at baseline, only LTPA classified as heavy or vigorous was independently associated with a reduction in all-cause mortality and reduced risks of premature death from CVD including CHD (Yu et al., 2003).

Reasons for discrepancies between studies with regard to the significance of the duration and intensity of exercise include the definition of vigorous exercise used in various studies and the number of times per week and length of study. In shorter-term studies, only higher intensities of physical activity may be related to reduction in all-cause and CVD-related mortality. In longer term studies, the relationship of moderate exercise intensity may become more apparent.

Physical activity may Modify Risk for Cardiovascular Disease and Morbidity through its Effect on other Risk Factors.

The beneficial effects of LTPA in reducing all-cause mortality and CVD-related mortality may be mediated through its effect on various risk factors. Physical activity has been associated with reduction in the incidence of several risk factors including diabetes, hypertension, smoking status and BMI. Higher BMI values and diabetes were associated with increased CHD risk after controlling for age and LTPA energy expenditure (Haapanen et al, 1997). The relationship between physical activity and CHD was examined over a 23-year period in men of Japanese heritage in the Honolulu Heart Program (Rodriguez, Curb, Burchfield, Abbott, Petrovitch, Masaki, et al., 1994). The Framingham physical activity index was used to assess physical activity level duration and intensity. Individuals in the highest tertile for physical activity had a significant reduction in risk for CHD and death from CHD compared to men in the lowest physical activity group. However, when relative risk was adjusted for age, hypertension, smoking, alcohol intake, diabetes, cholesterol, and BMI, the relationship between physical activity and CHD mortality was no longer significant suggesting that the beneficial effects of physical activity were due to the effects of physical activity in reducing hypertension, diabetes, cholesterol levels and BMI (Rodriguez et al., 1994).

The Relationship between BMI and Cardiovascular Disease

Body weight, body fatness and the pattern of fat deposition appear to be related to the risk for CVD. Body mass index (BMI) is a measure of an individual's body weight

relative to height. It is calculated as the quotient of body weight in kilograms divided by height expressed as square meters. Values of 25 kilograms per square meters of height (kg/m^2) or greater are considered overweight and values greater than 30 kg/m^2 are considered obese (Cheung, Machin, Karlberg, & Khoo, 2004). BMI is a widely used screening tool for assessing an individual's risk for disease and as BMI increases above 25 kg/m^2 there is an exponential increase in mortality rate and risk of CVD.

BMI data from the third National Health and Nutrition Examination Survey (NHANES III) showed that approximately 63% of men and 55% of women in the United States were overweight or obese (Must, Spadano, Coakley, Field, Colditz, & Dietz, 1999). Overweight and obese men have an excess risk of CHD as well as overall mortality (Yarnell, Patterson, Thomas, & Sweetman., 2000). Lack of physical activity, as well as overweight and obesity, are related to an increased incidence of CVD (Anderson. et al., 1997 & Takami, Takeda, Hayashim, Sasaki, Kawachi, Yoshino, et al, 2001). Regular physical activity may prevent body mass gain, which is primarily due to an increase in body fat, in adults. Physical inactivity is a risk factor for body mass gain and obesity among adults (Haapanen et al., 1997). A decrease in body fat as a result of physical activity also attenuates the development of CVD (Colbert, et al., 2004).

The Framingham Heart Study, which followed individuals who were 35 to 75 years of age over a 44-year period, demonstrated that CVD-risk was increased in overweight and obese men and women compared to men and women of normal weight (Wilson, D'Agostina, Sullivan, Parise, & Kanne., 2002). In the Caerphilly Prospective Study, men aged 45 to 59 years were followed over a 14-year period in order to examine

the influence of weight change on mortality and coronary events. Study participants were asked their weight at 18 years of age. This weight was compared to their current body weight and their body weight after 14 years of follow-up. Men with BMI values of 30 kg/m^2 or greater were shown to be at a greater risk for CHD and overall mortality (Yarnell et al., 2000).

In the Whitehall study of London-based male government employees with and without prevalent CHD, 18,403 middle-age men were followed for up to 35 years (Batty et al., 2005). In men with CHD as well as healthy men at entry into the study, overweight men had a moderately greater risk for all-cause mortality and CHD mortality. Mortality rates also were increased in the obese group. Avoidance of overweight and obesity in adult life in both men with and without CHD may reduce the risk of total and CHD mortality (Batty et al., 2005).

The risk of death from CHD and all causes associated with BMI and weight gain from age 20 to middle age was assessed in 6,874 men, aged 47 to 55 years at baseline (Rosengren et al., 1999). All men were free of a history of myocardial infarction and were followed for non-fatal myocardial infarction for an average of 11.8 years. Participants also were followed for CHD-related mortality and all-cause mortality over an average period of 19.7 years. BMI greater than 27.5 m/kg^2 predicted death from CHD. Men with stable weight (defined as $< \pm 4\%$ change from age 20) had the lowest risk of non-fatal myocardial infarction and the lowest death rate. Men who increased body weight more than 35% had a relative risk of 3.35 for non-fatal myocardial infarction after adjustment for age, physical activity, and smoking compared with men of stable body

weight. The relative risk of death from CHD was 1.57 (after adjustment for age, physical activity, and smoking) in the group that gained 4 to 10% to 2.76 in the group that gained more than 35% compared to men with stable weight. Relative risks were reduced but still significantly elevated in all weight gain groups after adjustment for serum cholesterol, systolic blood pressure, and diabetes. Weight gain from 20 years of age, even a very moderate increase, is strongly associated with an increased risk of non-fatal myocardial infarction and death related to CHD.

The relationship between being overweight or obese and mortality and morbidity were examined in the Caerphilly Prospective Study (Yarnell et al., 2000). Males reporting BMI values of 30 kg/m^2 or greater at 18 years of age had an increased risk for all-cause and CHD-related mortality during 14 years of follow-up when aged 45 to 59 years compared with non-obese men after adjustment for age, smoking habit and social class. The effect of weight gain from 18 years of age to recruitment was examined also. Weight gain during this period was strongly associated with potential cardiovascular risk factors measured at recruitment, including insulin, triglyceride, glucose, diastolic and systolic blood pressure and high-density lipoprotein-cholesterol (Yarnell et al., 2000).

Higher values of BMI were related to increased risk of new CHD when adjusted for age, smoking habit and social class in the Caerphilly and Speedwell population cohorts of men who were 45 to 59 years of age upon entry in the study (Yarnell, Patterson, Sweetman, Thomas, Bainton, Elwood, et al., 2001). Also, individual skinfold measurements (biceps, triceps, subscapular and abdominal skinfolds) and the sum of four skinfolds were significantly associated with risk of new CHD when BMI was excluded

from the regression model. However, only the subscapular skinfold measurement was related independently to risk of subsequent CHD when BMI was included in the regression model (Yarnell, Patterson, Thomas, & Sweetman., 2001). Individuals in the upper quintile of subscapular skinfold thickness had almost a doubling in the likelihood of CHD compared to individuals in the lowest quintile after adjustment (Yarnell et al., 2001). This suggests that BMI and skinfold thickness are closely related, which might be expected since BMI values would increase as body fatness increases. Although general skinfold measurements contributed only marginally to improved prediction of risk of CHD as measured by BMI, central obesity assessed by the subscapular skinfold measurement was predictive of CHD independently of BMI (Yarnell et al., 2001).

Although the majority of studies show an increased risk of CVD with higher BMI values, one important study is not consistent with this relationship. Self-reported BMI was not an independent risk factor for mortality from CVD, CHD or from all causes during 16 years of follow-up in men and women aged 35 to 63 years upon entry into the study (Haapanen-Niemi et al., 2000).

Blood Lipids and Cardiovascular Disease

Many studies have established that serum cholesterol is a strong predictor of CVD (Anderson et al., 1987; Benfante & Reed, 1990; Huxley et al., 2002; Martin et al., 1986). Furthermore, elevated levels of low-density lipoprotein-cholesterol (LDL-C) and triglycerides have been associated with the progression of CVD, while high-density lipoprotein-cholesterol (HDL-C) levels are inversely associated with CVD (Huxley et al., 2002; Nicholls et al., 2002). In the Framingham Offspring Study of men, aged 35 to 54

years, total cholesterol, LDL-C and HDL-C has strong associations with the prevalence of CHD (Wilson et al., 1980). The total cholesterol/HDL cholesterol ratio also had a robust relationship with CHD. In the Framingham Study, HDL-C levels were inversely related to development of CHD in both men and women aged 49 to 82 years, who were followed up to 12 years (Castelli, Garrison, Wilson, Abbott, Kalousdian, & Kannel, 1986). Participants at the 80th percentile of HDL-C had one-half the risk of CHD compared with subjects at the 20th percentile of HDL-C (Castelli et al., 1986).

In the Caerphilly and Speedwell population cohorts of men, 45 to 63 years of age, fasting triglycerides, total cholesterol and HDL-C were strongly and independently predictive of CHD after 10 years of follow-up (Yarnell et al., 2001). In a cohort of 8,006 men of Japanese ancestry, serum cholesterol and LDL-C levels measured during middle age were predictive of incident CHD in elderly men 65 years of age and older (Reed & Benfante, 1992). Although HDL-C had a protective effect against the incidence of CHD, it was not a significant predictor of CHD in the elderly. Serum triglyceride level was not a significant predictor of CHD for the elderly,

The risks associated with various levels of serum cholesterol were determined by analysis of 6-year mortality in 361,662 men 35 to 57 years of age (Martin et al., 1986). Above the 20^{th} percentile for serum cholesterol (> 4.68 mmol/l), CHD mortality increased progressively. The relative risk was very high (3.8) in men with cholesterol levels above the 85^{th} percentile (> 6.54 mmol/l). When men below the 20^{th} percentile were used as the baseline risk group, one-half of all CHD deaths were associated with elevated serum cholesterol concentrations, and one-half of these excess deaths were in

men with cholesterol levels above the 85th percentile (Martin et al., 1986). In the Primary Prevention Study in Goteborg, Sweden, men, aged 51 to 59 years at entry into the study, with serum cholesterol levels greater than 7.2 millimoles per liter (mmol/l) had a 2½-fold greater risk of death related to CHD compared to men with cholesterol levels lower than 5.2 mmol/l during 16 years of follow-up (Rosengren et al., 1997).

For older individuals, several prospective population studies have reported significant, positive correlations between the incidence of coronary events and serum total cholesterol or LDL-C; however, in several studies the strength of the relationship between cholesterol and CHD was weaker for older individuals (Kannel, Castelli, & McNamara, 1971; Maniolo, Pearson, Wenger, Barrett-Connor, Payne, & Harlan, 1992) or absent (Krumholz, Seeman, Merrill, Mendes de Leon, Vaccarino, 1994). In the Framingham Heart Study, the risk ratio for CHD between participants in the highest and lowest quartiles of total cholesterol were 3.6 for men younger than 50 years of age, but 2.2 for men greater than 50 years of age (Kannel et al., 1971). A later report from the Framingham study followed total and CVD mortality over a 30-year period in a large cohort of healthy men and women between 31 and 65 years of age (Anderson et al., 1987). For participants under 50 years of age, cholesterol levels were directly related to overall and CVD mortality; the CVD death rate increased 9% for each 10 mg/dL increase in serum total cholesterol. In participants older than 50 years of age, total mortality was not different in individuals with either high or low serum cholesterol levels; however, a direct association between falling cholesterol levels over the first 14 years and mortality over the following 18 years may have confounded the results. Overall mortality increased

11% and the CVD death rate increased 14% per 1 mg/dL per year drop in cholesterol levels. For individuals younger than 50 years of age, low total cholesterol levels were associated with decreased total and CVD-related mortality, but after age 50 years of age the association of mortality with cholesterol values likely was confounded by participants whose cholesterol levels were falling, perhaps due to diseases predisposing these persons to death (Anderson et al., 1987).

In the Honolulu Heart Program serum cholesterol levels were an important predictor for CHD when measured after age 65 (Benfante, Reed, & Frank, 1992; Reed & Benfante, 1992). The relationship between serum cholesterol and the 12-year incidence of CHD was examined among 3,440 middle-aged men (51 to 59 years of age) and 1,419 elderly men (65 to 74 years of age) at baseline examination. Serum cholesterol level was a significant predictor of CHD for both age groups. While the relative risk between serum cholesterol and CHD was similar between middle-aged and elderly men, the excess risk was typically between 1.5 to 2.0 times higher for the older than the middle-aged men (Benfante et al., 1992).

In a cohort of elderly individuals, greater than 70 years of age, participating in the Established Population for the Epidemiologic Study of the Elderly (EPESE) in New Haven, Connecticut, elevated total serum cholesterol level, low HDL-C, and high total serum cholesterol to HDL-C ratio were not associated with a significantly higher rate of all-cause mortality, CHD mortality, or hospitalization for myocardial infarction or unstable angina after adjustment for cardiovascular risk factors (Krumholz et al., 1994). The relationship of CHD with total and LDL-C was examined during 129 months of

follow-up in a cohort of men and women of 60 years of age and older (Simons, Simons, Friedlander, & McCallum, 2001). Total cholesterol, LDL-C, and total cholesterol/HDL-C were significant predictors of CHD only in the cohort of individuals who were 60 to 69 years of age, but not in cohorts who were 70 to 79 years of age or older than 80 years (Simons et al., 2001). In a prospective, population-based study of adults, 65 years of age and older, conducted at four field centers in U.S. communities with 7.5 years of follow-up, the relationships between total cholesterol and LDL-C and myocardial infarction were only marginally significant; however, the association between low HDL-C and increased risk of myocardial infarction was robust and consistent (Psaty, Anderson, Kronmal, Tracy, Orchard, Fried, et al., 2004).

In a study that pooled risk estimates across 25 populations from 22 U.S. and international cohort studies (Manolio et al., 1992), the relative risk of fatal CHD in relationship to either total cholesterol or LDL-C was significant across a broad range of ages up to 65 years of age. The relative risk of fatal CHD in relation to total cholesterol and LDL-C, although still significant, was weakened with advancing age, especially in women. HDL-C levels were inversely associated with CHD in middle-aged men and women and in older women, but not in older men (Maniolo et al., 1992). Weakened relationships between total cholesterol or LDL-C in elderly individuals may be due to the effect of previous selection during the decades prior to study when individuals with favorable genetics, i.e. those likely to survive despite elevated total or LDL cholesterol, survived while individuals with less favorable genetics did not survive (Tikhonoff, Casiglia, Mazza, Scarpa, Thijs, Pessiana, & Staessen, 2005).

Use of traditional cardiovascular risk factors, such as cholesterol, is imprecise and predicts less than one half of future cardiovascular events (Rasouli et al., 2005). Overt hyperlipidemia is present in fewer than half of all patients who have myocardial infarctions (Blake & Ridker, 2001), suggesting that other factors must contribute to CVD. Cholesterol levels were not a predictor of progression of coronary calcium, a measure of coronary plaque burden, in older individuals (mean age 61 years) followed over eight to 80 months (Rasouli et al., 2005). CRP and homocysteine levels demonstrated a stronger relationship than cholesterol levels with progression of CAD (Rasouli et al., 2005). CAD has a significant inflammatory component (Libby & Theroux, 2005), and recent studies have focused on whether plasma levels of inflammatory markers can assist in prediction of individuals at increased risk of plaque rupture (Ridker, 1999).

Blood Lipids, Physical Activity, BMI and Heart Disease

Physical activity may reduce both body fatness and BMI as well as blood lipids. Both of these effects may result in a reduced risk for CVD. Aerobic exercise was effective for decreasing total cholesterol, LDL-C, and triglycerides and increasing HDL-C in women (Kelley et al., 2004). Data from the Women's Ischemia Syndrome Evaluation (WISE) study found that higher physical fitness scores using the self-reported Duke Activity Standard Index (DASI) were independently associated with fewer CAD risk factors, less angiographic CAD, and lower risk for adverse cardiovascular events in women undergoing coronary angiography for suspected ischemia (Wessel, Arant, Olson, Johnson, Reis, Sharaf, et al., 2004). Women who had lower DASI scores were more likely to have more risk factors for CAD, although each 1-MET increase in DASI scores

resulted in an 8% decline for risk of major adverse cardiovascular events during follow-up. Although overweight women were more likely than normal weight women to have CAD risk factors, neither BMI nor abdominal obesity measures were significantly associated with obstructive CAD or adverse cardiovascular events after adjusting for other risk factors. Measures of obesity were not independently associated with these outcomes (Wessel et al., 2004).

There is a close association between physical activity, overweight and obesity, cholesterol levels and risk for CHD (Garrison, Wilson, Castelli, Feinleib, Kannel, & McNamara, 1980). In Japanese-American men, aged 71 to 93 years, from the Honolulu Heart Program, physical activity was positively associated with HDL cholesterol, while BMI and subscapular skinfold thickness were negatively associated (Burchfiel, Abbott, Sharp, Curb, Rodriguez, & Yano, 1996). Physical activity was associated with lower triglyceride levels, while higher BMI and subscapular skinfold thickness was associated with higher triglyceride levels. The relationship between physical activity or physical fitness and decreased risk of all-cause and CVD-related mortality may be due in part to a physical activity mediated reduction in total and LDL cholesterol, increase in HDL-C, and reduction in body fatness and BMI.

Serum Glucose, BMI and Physical Activity

Obesity is associated with an increased risk of morbidity and mortality as well as reduced life expectancy (Poirier & Despres, 2006). Overweight and obesity may affect the heart and cardiovascular system through its influence on many risk factors, such as dyslipidemia, glucose intolerance, inflammatory markers, hypertension and promotion of

a prothrombotic state (Poirier & Despres, 2006). Higher blood glucose levels are an indicator of impaired glucose tolerance or increased resistance to insulin. Elevated blood glucose had been linked to an increased risk of CVD (Bowman & Armitage, 2002: Petersen & McGuire, 2005; Schnell, 2005). For example, CVD is a major cause of the reduction in life expectancy in patients with diabetes (Schnell, 2005). Seventy-five percent of diabetic patients die prematurely of cardiovascular complications. Both prediabetes and diabetes highly pre-dispose to cardiovascular alterations, and even serum glucose levels at the upper end of the normal range may predispose individuals to an increased risk of CVD (Schnell, 2005). Very importantly, elevated serum glucose levels have been linked with low grade inflammation (Barzilay & Freedland, 2003). Decreasing overweight and obesity, as well as participation in physical activity, may improve serum glucose levels and reduce the risk of CVD.

Inflammation, C-Reactive Protein and Cardiovascular Disease

As discussed previously, it is now recognized that not only lipids, but inflammation plays an important role in the development of atherosclerosis (Blake & Ridker, 2001, 2002; Koenig et al., 2003). There is compelling evidence that local and systemic inflammatory responses play key roles in the development of CVD (Danesh, Whincup, Walker, Lennon, Thomson, Appleby et al., 2000; Koenig, Sund, Frohlich, Fischer, Lowel, Doring, et al., 1999). Inflammatory processes may mediate many of the stages of atheroma development from initial leukocyte recruitment to eventual rupture of the unstable atherosclerotic plaque. Atherosclerosis, which underlies CHD, myocardial infarction, ischemic stroke, and peripheral vascular disease, is linked in part to chronic,

low-level inflammation of the vascular endothelium (Blake & Ridker, 2002, Danesh et al., 2000; Ross, 1999, Scott, 2004)

Plasma levels of several markers of inflammation have been shown to be associated with future CVD risk in a variety of clinical settings (Blake & Ridker, 2002). These markers include CRP, homocysteine, cell adhesion molecules, cytokines, pro-atherogenic enzymes, serum amyloid-A, tumor necrosis factor-α (TNF- α), interleukin-6 (IL-6) and fibrinogen.

The Influence of C-Reactive Protein on Cardiovascular Disease

CRP is a member of a family of nonspecific, acute-phase reactant proteins (Gabay & Kushner, 1999), and is a highly sensitive and objective marker of inflammation, tissue damage and infection (Koenig et al., 2003). CRP is normally present in the circulation at very low levels, but acute inflammatory processes, infections, or tissue injuries induce marked increases in hepatic synthesis of CRP that can induce a 100-fold increase in serum levels (Du Clos, 2000). Evidence also shows that arterial plaque can produce CRP, independent of traditional hepatic pathways. Smooth muscle cells and macrophages within the atherosclerotic plaque are sources of CRP (Vainas, Stassen, De Graaf, Twiss, Herngreen, Weltem, et al., 2005; Yasojimz, Scwab, McGeer, & McGeer, 2001). Additionally, coronary plaques, aneurysmal aortas, failed venous coronary bypasses, and femoral plaques also produce CRP, thus illustrating that the production of CRP may represent a universal response to vascular injury and suggesting that vascular CRP may contribute to plaque development (Vainas et al., 2005).

Initially thought of as an inactive downstream marker in the inflammatory cascade, emerging evidence suggests that CRP may be directly involved in atherogenesis (Blake & Ridker, 2001; Koenig et al., 2003). Furthermore, CRP has been demonstrated to actively contribute to all stages of atherogenesis, participating in endothelial dysfunction, atherosclerotic-plaque formation, plaque maturation, plaque destabilization and eventual rupture (Verma, Szmitko, & Ridker., 2005). The presence of inflammation as demonstrated on autopsy in patients with lethal myocardial infarctions through the accumulation of monocytes and macrophages at the sites of plaque rupture, suggests that inflammatory markers such as serum CRP levels may reflect the atherosclerotic process and could potentially help identify those at risk of future events (Wilcox, Abbott, Yano, Rodriguez, Willcox, Tanaka, et al., 2004).

Data supporting the role of CRP for cardiovascular risk prediction in apparently healthy individuals are robust and remarkably consistent across several studies in Europe and the United States (Ridker, Hennekens, Buring, & Rifai., 2000; Kuller, Tracy, Shaten, & Meilahn, 1996; Koenig, Sund, Frohlich, Fischer, Lowel, Doring, et al., 1999; Tracy, Lemaitre, Psaty, Ives, Evans, Cushman, et al., 1997; Ridker, Glynn, & Hennekens, et al., 1998). Multiple prospective studies in the United States with middle-aged men (*e.g.,* the Honolulu Heart Program, (Curb, Abbott, Rodriguez, Sakkinen et al. 2003; Sakkinen, Abbott, Curb, Rodriguez, Yano, & Tracy, 2002), Physicians' Health Study (Ridker, Cushman, Stampfer, Tracy, & Hennekens., 1997; Ridker et al., 1998), and Multiple Risk Factor Intervention Trial (MR FIT) (Kuller et al., 1996)), postmenopausal women *(e.g.,* the Women's Health Study (Ridker et al., 2000, Ridker et al., 1998)), and elderly men and

women (*e.g.*, the Cardiovascular Health Study and Rural Health Promotion Project (Tracy et al., 1997)) have shown that CRP is a strong, robust, and independent risk factor for CVD. Additional studies of middle-aged men in the United Kingdom (Mendall et al., 1996), Germany (MONICA Study, Koenig et al., 1999), and Finland (Roivainen, VViik-Kajander, Palosuo, Toivanen, Leinonen, Saikku, et al., 2000) support the US findings. Baseline levels of CRP are a strong and independent predictor for risk of myocardial infarction, stroke, peripheral vascular disease, as well as death from stroke and vascular disease among healthy individuals (Blake & Ridker, 2002; Vainas et al., 2005). Serum CRP has been shown to be an independent marker of the extent of atherosclerosis in patients with coronary, cerebrovascular, and peripheral arterial disease. CRP is an independent determinant of stroke (Curb et al. 2003), which is a form of CVD, among both men and women.

The association between CRP and CHD were examined in a large combined analysis from the Caerphilly and Speedwell population cohorts (Lowe, Sweetman, Yarnell, Rumley, Rumley,Bainton, et al., 2004). Men, aged 49 to 66 years, were studied between 1982 and 1988 and re-examined for new CHD events at fixed intervals of approximately 105 months (Caerphilly study) and 75 months (Speedwell study) (Lowe et al., 2004). Mean levels of CRP were significantly higher among men who developed CHD. Men in the top 20% of the CRP distribution had a three-fold increase in the relative risk for CHD.

The relationship of serum CRP with the incidence of the first major CHD event was examined in 936 men, 45 to 64 years of age, over an eight-year period in the

MONICA (Monitoring of Trends and Determinants in Cardiovascular Disease) study (Koenig et al., 1999). CRP values showed a strong positive relationship with the incidence of CHD events. After adjustment for age, the hazard rate ratio for CHD was 1.60, and the relationship remained significant after adjusting for smoking behavior. It was concluded that CRP was closely related to the risk of CHD in a large, randomly selected cohort of initially healthy middle-aged men (Koenig et al., 1999).

Serum hsCRP (high sensitivity CRP) showed a significant inverse relationship with the ankle-brachial pressure index (ABPI) at baseline and at 12-month follow-up in subjects with peripheral artery disease (Vainas et al., 2005). ABPI is used as an indication of severity of peripheral artery disease. Subjects were divided into three groups of equal size according to baseline serum hsCRP levels. ABPI at baseline and at 12-months was greatest in individuals with the lowest hsCRP levels and least in the subjects with the highest hsCRP levels. Also, serum hsCRP was related to the combined end point "death and/or any cardiovascular event" during a median 24-month follow-up period, suggesting a relationship between hsCRP levels and hemodynamic function and future cardiovascular events in patients with peripheral artery disease (Vainas et al., 2005).

In the Women's Health Study, measurements of CRP and LDL-C were taken at baseline in 27,939 apparently healthy women, who were followed for a mean of eight years for the occurrence of myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes (Ridker, Rifai, Rose, Buring, & Cook, 2002). Although there was a minimal relationship between CRP and LDL, the baseline levels of each had a strong linear relationship with the incidence of

cardiovascular events. CRP and LDL-C measurements tended to identify different high-risk groups. Seventy-seven percent of all cardiovascular events occurred among women with LDL-C levels below 4.14 mmol/liter (160 mg/dl), and 46 percent occurred among those with LDL-C levels below 3.36 mmol/liter (130 mg/dl) (Ridker et al., 2002). It was concluded that CRP level was a stronger predictor of cardiovascular events than the LDL-C level (Ridker et al., 2002). Most importantly, the relative magnitude of hsCRP predictive ability appears to outweigh that of other novel risk factors, including homocysteine and lipoprotein (a) (Ridker et al., 2000; Ridker et al 2001).

Additional studies show a consistent positive association between CRP and future cardiovascular events in both initially healthy subjects and patients with angina pectoris (Danesh et al., 2000). The occurrence of fatal and non-fatal CHD and the relationship to CRP was examined in 506 men who died from CHD or had a non-fatal myocardial infarction and 1,025 men who remained free of such disease until 1996. Compared with men in the bottom third of CRP levels at baseline, men in the top third had over a two-fold greater risk of CHD after adjusting for age, town, smoking, vascular risk factors, and indicators of socioeconomic status (Danesh et al., 2000).

The association of CRP with incident CHD among middle-aged adults in the Atherosclerosis Risk In Communities (ARIC) study was examined in a prospective study (Folsom, Aleksic, Catellier, Juneja, & Wu, 2002). CRP levels in two groups of subjects, who developed CHD during 5 to 6 years of follow-up, were compared with two stratified random samples of subjects without CHD. The relative risk of CHD was one and one-half- to almost two-fold greater in the three highest quintiles of CRP compared with the

two lowest CRP quintiles. This demonstrates that CRP was a moderately strong marker of risk of CHD in this cohort of middle-aged adults, which is consistent with the role of inflammation in the pathogenesis of CHD events (Folsom et al., 2002).

Results from the Honolulu Heart Program suggest that the relationship between CRP levels and the risk of CVD may be stronger in men at low risk for CVD compared with those whose risk is higher (Sakkinen et al., 2002; Curb et al., 2003). The estimated risk of thromboembolic stroke increased significantly with rising CRP levels in middle-aged men, in men without hypertension or diabetes, and in those who were never cigarette smokers. For middle-aged men, there was a three-fold increase in the occurrence of a thromboembolic stroke in men in the highest quartile of CRP levels compared with men in the lowest quartile for CRP levels. In nonsmokers, there was a nearly six-fold increase in thromboembolic stroke in men in the highest quartile of CRP levels compared with men in the lowest quartile for CRP levels. The relationship between CRP and stroke was independent of total cholesterol, BMI, alcohol intake, physical activity index, and other risk factors. In contrast, the relationship between CRP levels and risk of thromboembolic stroke were not as strong and were not significant in less healthy men or those with other risk factors including past and current smokers, men greater than 55 years of age, and in men with hypertension or diabetes.

Similar to the association between CRP and stroke, the relationship between CRP and myocardial infarction were stronger in middle-aged men, men without hypertension or diabetes, and in those who were nonsmokers. Although small sample sizes could have weakened the capacity to detect an association between CRP and myocardial infarction in

higher-risk individuals, other studies have reported a stronger relationship between CRP and CVD in nonsmoking women and in women without hypertension or diabetes compared with women who smoked or were hypertensive or diabetic (Ridker et al., 1998). In apparently healthy individuals who have an absence of many more conventional risk factors, CVD can still occur (Rost, Wolf, Kase, Kelly-Hayes, Silbershatz, Massaro, et al., 2001). In these individuals, the effects of inflammation may have overriding importance in the development of CVD. The weaker association in older or less healthy men and women could have several explanations. Although inflammation may still be important, in the presence of other risk factors a high risk of CVD could mask any residual, and perhaps weaker, effects of inflammation.

In a subgroup from the Caerphilly study, there was a positive association between CRP and incident ischemic heart disease, mainly with fatal disease (Mendall, Patel, Ballam, Strachan, & Northfield., 2000). CRP was significantly associated with several risk factors including BMI, smoking and age. Interestingly, after adjustment for various risk factors including BMI, smoking, low forced expiratory volume, height, low childhood social class and age the association with all-incident ischemic heart disease and ischemic heart disease death became non-significant, suggesting that although CRP levels are raised in association with a variety of established cardiovascular risk factors, neither CRP nor the systemic inflammation it represents appears to play a direct role in the development of ischemic heart disease (Mendall et al., 2000).

A prospective, nested, case-control analysis involving 97 cases of sudden cardiac death (SCD) among apparently healthy men enrolled in the Physician's Health Study was

completed in order to compare the relative importance of CRP, homocysteine, and lipids as long-term predictors of SCD (Albert, Ma, Rifai, Stampfer, & Ridker, 2002). Only baseline CRP levels were significantly associated with the risk of SCD over the ensuing 17 years of follow-up. The increase in risk associated with CRP levels was primarily seen among men in the highest quartile, who had a 2.78-fold greater risk of SCD compared with men in the lowest quartile (Albert et al., 2002). In contrast to the positive relationship observed for CRP, neither homocysteine nor lipid levels were significantly associated with risk of SCD (Albert et al., 2002).

Based on the results of many prospective epidemiologic studies, CRP has emerged as one of the most powerful predictors of CVD (Verma, Szmitko, & Ridker, 2005). CRP shows significant correlations with other established risk factors for CVD, including age, systolic and diastolic blood pressure, smoking, BMI, physical inactivity, total and HDL-C, triglycerides, and homocysteine (Rohde, Hennekens, & Ridker, 1999). The predictive ability of hsCRP may even surpass that of LDL-C and/or the total cholesterol-to-HDL-C ratio, currently the main CVD assessment tools (Ridker et al., 1998; Rifai & Ridker, 2001). Screening for both LDL-C and CRP may provide better prognostic information than screening for either alone. Finally, adding hsCRP to total high-density lipoprotein cholesterol ratio significantly improves the predictive ability of both tests.

Physical Activity, Body Mass Index, C-Reactive Protein and Risk of Cardiovascular Disease

As discussed previously, many studies have demonstrated that higher levels of regular physical activity or cardiorespiratory fitness are associated with a reduced risk of CVD. Also, increased adiposity, especially increased amounts of visceral fat, as evidenced by increased values for BMI or WHR are related to greater risk for CVD. Both lack of physical activity and increased adiposity appear to be linked to increased systemic inflammation. In men and women classified with metabolic syndrome, based on NCEP ATP III criteria, as well as individuals without metabolic syndrome, levels of CRP, serum amyloid-A, TNF-α, IL-6 and fibrinogen were lower in individuals reporting LTPA compared with those reporting no LTPA (Pitsavos, Panafiotakos, Chrysohoou, Kavouras, & Stefanadis, 2005). Findings from Tamakoshi et al. (2002) suggest that being overweight or obese increases CRP levels: therefore increasing the likelihood of CVD. More specific discussions regarding the potential roles of CRP and homocysteine with respect to CVD, and their association with physical activity and adiposity are presented in the following sections.

Results of studies examining the effect of regular physical activity on CRP levels are somewhat equivocal. Cross-sectional studies suggest that physical activity reduces CRP levels (Colbert et al., 2004; Reuben, Judd-Hamilton, Harris, & Seeman, 2003), but results from longitudinal studies are inconsistent. Cross-sectional data from the Health, Aging and Body Composition Study showed lower CRP levels in elderly individuals, 70 to 79 years of age, reporting greater than 180 minutes of exercise per week compared with those reporting no exercise (Colbert et al., 2004). Adjustment for body fatness

attenuated the relationship between exercise and CRP slightly. Among individuals who did not participate in regular exercise, individuals reporting greater physical activity had lower CRP levels compared to those who reported less physical activity (Colbert, et al., 2004). The relationships between recreational activity, house/yard work activity, work activity, and total physical activity and CRP levels were examined in a cross-sectional study of individuals, aged 70 to 79 years, who were in the top third of community-dwelling older persons with respect to physical and cognitive functioning (Reuben et al., 2003). Both self-reported recreational activity or house and yard work activity were independently associated with lower CRP levels. The association between high levels of recreational activity and lower levels of CRP suggest a mechanism for the protective effect of physical activity (Reuben et al., 2003).

The HERITAGE longitudinal study reported that CRP levels were reduced with exercise training in individuals with high initial CRP levels (Lakka et al., 2005). High sensitivity CRP was measured before and after a 20-week exercise training program in 652 sedentary healthy white and black men and women (Lakka et al., 2005). The study sample was stratified according to baseline CRP levels using a recommended classification system (low <1.0 mg/L; moderate 1.0-3.0 mg/L; high >3.0 mg/L). The median decline in CRP was 1.34 mg/L in the high baseline CRP, but CRP levels did not change in the groups with low or moderate CRP levels at baseline.

CRP levels were unchanged in middle-aged men with aerobic exercise training over a six year period in the DNASCO study (Rauramaa et al., 2004), The progression of atherosclerosis in middle-aged men was followed during a 6-year randomized, controlled

trial in Eastern Finland. Men participated in low- to moderate-intensity aerobic exercise. Atherosclerosis was quantified using the mean intima-media thickness of the carotid artery using ultrasonography at baseline and at years two through six. High sensitivity CRP levels were measured as a marker for inflammation. The progression of intima-media thickness in the carotid artery did not differ between exercise and control groups, and hsCRP levels were similar for the two groups. However, an analysis of a subgroup of men who were not taking statin drugs showed that the 6-year progression of intima-media thickness, adjusted for smoking and LDL-C level, systolic blood pressure, and waist circumference, was 40% less in the exercise group (Rauramaa et al., 2004). Exercise training did not have a significant effect on CRP in overweight or obese, BMI $\geq$ 28 kg/m^2, sedentary men and women, aged 60 years or older (Nicklas, Ambrosius, Messier, Miller, Penninx, Loeser, et al., 2004). Subjects participated in combined weight training and walking for one hour, three days per week.

Any relationship between physical activity or exercise and CRP levels may be due at least in part to the effects of physical activity and exercise on adiposity and BMI. In the beta-Blocker Cholesterol-Lowering Asymptomatic Plaque Study, individuals with greater BMI values had higher levels of CRP, but there was not a significant relationship between physical activity and CRP levels (Fredrikson, Hedblad, Nilsson, Alm, Berglund, & Nilsson, 2004). Subjects with a BMI greater than 27.6 kg/m^2 had 40% higher CRP levels compared with individuals with lower BMI values. (Fredrikson et al., 2004)

A diet-induced weight-loss intervention, involving a weekly session with a registered dietitian to provide education and support for lowering calorie intake, resulted

in significantly greater reductions in CRP levels compared with no weight-loss treatment (Nicklas et al, 2004). In a sample of obese, postmenopausal women, with mean age 56.4 years and a mean BMI of 35.6 kg/m^2, plasma CRP levels were positively associated with total body fatness and intra-abdominal body fat area (Tchernof et al., 2002). In a subgroup of who participated in a weigh loss protocol, there was a mean reduction in body weight of 14.5 kg, including a 10.4 kg reduction in fat mass. Visceral and subcutaneous fat areas were reduced by -36.4% and -23.7%, respectively. Plasma CRP levels declined 32%. Changes in body weight and in total body fat mass were both positively associated with plasma CRP level reductions (Tchernof et al., 2002).

Body fatness or BMI apparently explains a large part of the relationship between CRP and CVD risk. In a cross-sectional study of apparently healthy men and women, mean ages of 49.7 and 50.6, respectively, the Pearson correlation between hsCRP and the calculated 10-year Framingham Coronary Heart Disease Risk Score (FCRS) was lower when adjusted for BMI (Rogowski, Shapira, Toker, Melamed, Shirom, Berliner, et al., 2005). The reduction in the correlation was especially dramatic in women with a decline from 0.25 to 0.09. The correlation between hsCRP and the 10-year FCRS is partly related to the presence of obesity (Rogowski et al., 2005). Adiposity was strongly associated with low-grade systemic inflammation in men and in women, with a particularly strong relationship in women, especially for CRP (Thorand et al., 2006). In a cross-sectional analysis of 641 men and 597 women, aged 55 to 74 years, participating in the population-based KORA Survey 2000 in the area of Augsburg, Germany, measures of both total (fat mass, BMI) and abdominal adiposity (waist circumference and WHR) were highly

correlated with markers of systemic inflammation including CRP (Thorand et al., 2006). In women, percent body fat mass explained the highest percentage of the variability of circulating acute-phase proteins, but in men, WHR explained the highest percentage of the variability (Thorand et al., 2006).

In 405 healthy men and 454 healthy women from two large ongoing prospective studies, physical activity was inversely associated with plasma levels of CRP. After adjustment for BMI and leptin, as a surrogate for fat mass, most of these associations were no longer significant. These results suggest that frequent physical activity is associated with lower systemic inflammation, and that the relationship between physical activity and CRP can be explained partially by a lower degree of obesity in physically active subjects (Pischon, Hankinson, Hotamisligil, Rifai, 7 Rimm, 2003).

Homocysteine and Cardiovascular Disease

Homocysteine, a sulfur-containing metabolite of the amino acid methionine, is an inflammatory marker for CVD and may contribute to the development of CVD. Elevated plasma homocysteine concentrations are associated with a higher prevalence of CVD, including occlusive disease of the coronary, cerebral, and peripheral vessels (Aronow & Ahn, 2000; Kario, Duell, Matsuo, Sakata, Kato, Shimada, et al., 2001). Although cross-sectional and case-control studies consistently show an association between homocysteine and CVD, prospective studies have provided equivocal results (Cesari, Rossi, Sticchi, & Pessina, 2005).

Although the precise role of plasma homocysteine in CVD is unclear, homocysteine may induce the damage of the arterial wall and trigger the formation of

atherosclerosis. Homocysteine may contribute to endothelial dysfunction and damage, accelerated thrombin formation, inhibition of native thrombolysis, increased lipid peroxidation through free radical formation, vascular smooth muscle cell proliferation and monocyte chemotaxis (Splaver et al., 2004). Similar to CRP, homocysteine levels change when damaging effects occur on the arterial wall (Perna, Ingrosso, Lombardi, Acanfora, Satta, Cesare, et al., 2003), and increased homocysteine levels have been shown to cause vessel fibrosis. Elevated homocysteine apparently induces tissue injury by such mechanisms as oxidative stress, endothelial damage, and protein homocysteinylation. There is an elevation of homocysteine during acute myocardial infarction that may be related to an increase in the acute-phase reactant proteins (Senarante, Griffiths, & Nagendran, et al., 2000). It has been hypothesized that the link between homocysteine and CVD is mediated in part by activation of coagulation and endothelial cell injury (Kario et al., 2001).

Most, but not all, observational epidemiological studies indicate that individuals with higher homocysteine levels have increased risks of CVD and cerebrovascular events (Nurk et al., 2002; Verhoef, Meleady, daly, Graham, Robinson, & Boers, 1999). The magnitude ranges from approximately 20% in prospective studies to approximately 80% in retrospective case-control studies (Splaver et al., 2004). However, the amount of uncontrolled and uncontrollable confounding in all observational epidemiological studies is as large as the postulated small to moderate effect size of homocysteine (Splaver et al., 2004). Current evidence is necessary, but not sufficient to establish a cause-and-effect relationship between homocysteine and CVD.

Elevated plasma homocysteine concentration is considered a risk factor for CVD and may also be associated with hypertension (Dinhavahi & Falkner, 2004). Some reports describe a significant relationship between homocysteine and blood pressure levels, as well as higher homocysteine levels in hypertensive individuals compared to normotensive individuals. Other studies have reported that the effect of homocysteine disappears following adjustment for other risk factors. Because homocysteine cosegregates with other risk factors, it has been difficult to identify an independent effect of homocysteine on CVD or hypertension (Dinavahi & Falkner, 2004).

In elderly Japanese subjects, high homocysteine levels were independently related to CVD risk (Kario et al., 2001). After performing a 31-month follow-up on 500 men and women, homocysteine levels were found to be an independent predictor of CVD (Aronow and Ahn, 2000). In the Hordaland Homocysteine Study, participants with preexisting CVD had higher mean homocysteine levels at entry into the study compared to individuals without CVD (Nurk et al., 2002). Among subjects, aged 65 to 67 years at baseline, the risk of CVD hospitalizations increased significantly with increasing homocysteine levels. Following adjustment for multiple risk factors, elderly subjects with the highest homocysteine levels (> 20.0 μmol/l) were twice as likely as subjects with the lowest homocysteine levels (< 9.0 μmol/l) to be hospitalized for CVD. The relation between homocysteine level and CVD hospitalizations was significantly stronger among individuals with preexisting CVD than those without CVD. Although plasma homocysteine levels were a strong predictor of CVD hospitalizations in elderly individuals, especially those with preexisting CVD, there was not a statistically

significant relationship between homocysteine levels and CVD in middle-aged individuals (Nurk et al., 2002).

In a nested, case-control prospective study with extensive adjustment procedures, homocysteine was an independent risk predictor for CVD-related mortality (Blacher, Benetos, Kirzin, Malmejac, guize, & Safar, 2002). The adjusted hazard ratio for CVD mortality was 1.22 for each one standard deviation (3.9 μmol/L) increment of homocysteine (Blacher et al., 2002). A five-year study of physicians with elevated levels of homocysteine found a three-fold greater risk of CVD (Lee, Sesso, Oguma, & Paffenbarger, 2003).

Homocysteine was the strongest predictor of progression of CAD as assessed by coronary calcium in older individuals over an eight to 80 month follow-up (Rasouli et al., 2005). Individuals with elevated homocysteine ($\geq$ 12 μmol/L) demonstrated a mean increase in coronary calcium progression of 35% per year, while those with homocysteine less than 12 μmol/L progressed at 17% per year. Homocysteine was more closely related to CAD progression than CRP or cholesterol levels.

Physical Activity, Body Mass Index, Homocysteine and Risk of Cardiovascular Disease

Homocysteine levels have been shown to be associated to health-related behaviors, including physical inactivity, diet and smoking (Chrysohoou, Panafiotakos, Pitsavos, Zeimbekis, Zampelas, Papademetriou et al., 2004; Dinavahi & Falkner, 2004; Nurk, Tell, Vollset, Nygard, Refsum, Nilsen, et al., 2004). In the Hordaland Study, homocysteine levels were related to vitamin supplementation, smoking and changes in body weight (Nurk et al., 2004). The Hordaland study examined the effect of lifestyle

changes on homocysteine levels in 7,031 subjects who were either 41 to 42 years of age or 65 to 67 years of age at baseline. Homocysteine levels were measured upon entry into the study and six years later. Among the younger and older age groups, individuals who started to supplement with vitamins during the follow-up period had significant reductions in homocysteine concentrations (Nurk et al., 2004). In the younger subjects, smoking cessation resulted in a decline in homocysteine concentrations. Changes in body weight were inversely related to homocysteine. The changes noted in the Hordaland Homocysteine study, which used a longitudinal design, were modest when compared with the strong associations between homocysteine and lifestyle factors in cross-sectional studies (Nurk et al., 2004).

Homocysteine and Cardiovascular Fitness

Although cardiovascular fitness and homocysteine levels showed a significant inverse relationship in women, cardiovascular fitness and homocysteine levels were not association in men. A total of 1,444 adults, aged 20 to 49 years, with data collected from 1999 to 2002 from the National Health and Nutrition Examination Survey (NHANES) were used to examine the relationship between cardiovascular fitness and homocysteine (Kuo, Yen, & Bean, 2005). After adjustment for age, race and BMI, there was a 0.70 ml/kg/min decrease in the estimated VO_2max for each standard deviation increase in the natural-log-transformed homocysteine level for women. After additional adjustment of hypertension, diabetes, smoking status, alcohol intake, use of lipid-lowering agents, physical activity, self-reported health condition, as well as levels of folate, vitamin B_{12}, creatinine, CRP, total cholesterol and hemoglobin there was a 1.18 ml/kg/min decline in

the estimated VO_2max for each standard deviation increase in the natural-log-transformed homocysteine level in women (Kuo et al., 2005). There was no association between cardiovascular fitness and homocysteine levels in men. However, another study found fitness level, which was determined using maximal oxygen consumption, was inversely related to homocysteine levels in men but not women (Coombe et al., 2004). In a cross-sectional study of men and women, from the Athens, Greece area without a history of CVD, aerobic exercise was related with significantly lower homocysteine levels as compared to anaerobic or sedentary life although the magnitude of the difference (12%) was small (Panagiotakos et al., 2005)

In general, studies in adults have demonstrated a significant relationship between homocysteine and measures of body weight or adiposity. In young women, aged 25 to 30 years, and in older women, aged 60 to 65 years, homocysteine was positively associated with BMI (Rasmussen et al., 2000). BMI was not related to homocysteine in a cross-sectional study of healthy men and women, 40 to 67 years of age, with no history of hypertension, diabetes mellitus, CHD or cerebrovascular disease, (El-Khairy, Ueland, Nygard, Refsum, & Vollset, 1999). When comparing the relationship between homocysteine and BMI, an increase in BMI was related to an increase in homocysteine levels (Coombes, et al., 2004).

Conclusion

Many studies have found relationships between cardiovascular disease and inflammatory markers, physical activity, and BMI. From the information gathered, the relationship of these variables to cardiovascular disease is independent; each variable

may affect the others. For example, an increase in physical activity will decrease BMI and the occurrence of CVD. A six-year study performed by (Rauramaa et al. 2004) indicates that there was not a significant change in the levels of CRP as a result of exercise when comparing the control group to the testing group. One possible reason for this is that the control group was allowed to engage in physical activity. Thus, the control group's CRP level would not be very different because they would have been doing to the same routine as the testing group (Raramaa, et al., 2004). Overall, research has shown that each of these factors are related to CVD in a positive or negative way, but since less is known about the inflammatory markers, CRP and homocysteine, more research is needed to determine their relationship to CVD.

The purpose of this study was to determine the relationship between BMI and physical fitness, blood lipids, and inflammatory markers, as well as the relationship of these variables to cardiovascular disease using the NHANES database.

CHAPTER III

MATERIALS AND METHODS

Data Source

The National Health and Nutrition Examination Survey (NHANES) is a program of surveys and data collection designed to assess the health and nutritional status of adults and children in the United States. The survey includes interviews and physical examinations. NHANES is sponsored by the National Center for Health Statistics, which is a part of the Centers for Disease Control and Prevention (CDC) of the U.S. Public Health Service. NHANES data are available for public use.

The data used for the study were obtained by merging the 1999-2000 NHANES and the 2001-2002 NHANES data sets. Information for the database was gathered by the National Center for Health Statistics for the Centers for Disease Control and Health Statistics. Physical examinations performed on the participants were administered at Mobile Examination Centers (MEC) nationwide. Data collection involving medical and dental examinations, as well as physiological measurements and laboratory tests were conduction by a team of physicians and other highly trained medical personnel. The NHANES detailed interview included demographic, socioeconomic, dietary, and

health-related questions. Data from various surveys were used to determine the health and nutritional status of the population.

Participants

There were a total of 10,291 participants, aged 20 to 85 years, available from the 1999 through 2002 NHANES databases. Only 8,485 (82%) of these participants were included in the data analysis. Participants who were pregnant (n = 603), not examined at a mobile examination center (n = 820), or had missing values for height (n = 164) and/or weight (n = 125) were eliminated. The population used in this study was an adequate sampling of 20 to 85 year old individuals classified as non-Hispanic white, non-Hispanic black, Mexican-American, other Hispanic, and "others" that included multiracial in order to yield significant results. An informed consent form was given to each participant before they participated in the study.

Body Mass Index (BMI)

BMI was defined as body weight in kilograms divided by the square of height in meters and categorized into four groups: underweight ($\leq$ 18.5; n=144), normal weight (18.5 - 24.9; n= 2,542), overweight (25.0 – 30.0; n = 3,014), and obese ($\geq$ 30; n= 2,785) (Center for Disease Control and Prevention, 2003).

Physical Fitness

For cardiovascular fitness level, individuals were categorized as low, moderate, or high. Cardiovascular fitness was assessed using the heart rate response to a submaximal graded exercise test in order to estimate the individual's VO_2 max.

Dietary Folic Acid

Dietary folic acid intake was measured using a dietary interview questionnaire, which was given by telephone or a computer. The dietary intake data was used to estimate total intake of energy, nutrients, and non-nutrient food components from foods and beverages consumed over a 24-hour period prior to the interview (midnight to midnight). An NHANES computer-assisted dietary interview (CADI) system was the form used for data collection and was developed using Power Builder™; several databases (i.e., Quick List food list, brand name food list, and food amount unit list) that are linked to the system. The CADI system provided a standardized interview format to collect NHANES dietary interview data. The interviewers follow the prompts given by the system screens in order to explain the dietary interview components to the respondents.

C-Reactive Protein

For the NHANES database, serum CRP levels were measured using blood samples that had been collected from each participant. At least 0.3 milliliters of serum were collected. Participants were not required to fast before the blood sample was obtained. Blood samples were taken at MEC laboratories, and frozen at a temperature of -20° Centigrade. Samples were sent to the University of Washington for analysis. A Dade Behring Nephelometer II Analyzer System was used to measure CRP levels. (National Health and Nutrition Examination Survey [NHANES], 2001).

Homocysteine and Folate

Serum homocysteine and folate levels were measured using blood samples obtained from the participants at the mobile examination centers (MEC). Participants were required to fast before giving a blood sample to measure homocysteine levels. Once the serum samples were collected, they were shipped to the Division of Environmental Health Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention for analysis. Samples were stored at a temperature of -70 degrees Celsius for approximately 8 months to three years before analysis. An Abbot Homocysteine Assay was used to analyze the samples.

Serum total cholesterol, serum triglycerides, HDL-C, and Glucose

Serum total cholesterol, serum triglycerides, high-density lipoprotein levels, and serum glucose levels were measured using blood samples collected at the MEC. . Fasting blood samples were used for these analyses. Participants eligible for data collection must have fasted for at least 8 hours and no less than 24 hours. Blood samples collected at MEC laboratories were frozen at -20° Centigrade and sent to the Johns Hopkins University Lipoprotein Analytical Laboratory for analysis. Serum total cholesterol, HDL-C, triglycerides, and glucose were determined using a Hitachi Model 917 Multichannel Analyzer.

Statistical Analysis

The 1999-2000 NHANES and 2001-2002 NHANES data sets were merged and managed using SAS-callable SUDAAN statistical software (Research Triangle Institute, Cary, NC). SUDAAN procedures are used to analyze data from complex sample surveys and other observational and experimental studies. SUDAAN includes procedures for obtaining descriptive statistics and regression modeling. SUDAAN is a statistical program that accounts for the complex weighting of the survey data such as NHANES 99-02 sample.

For each variable, participant data were placed in the underweight, normal weight, overweight, or obese group. Group means and standard errors of the mean were calculated using SUDAAN software. Statistically significant differences between the following groups were determined using X^2-analysis: underweight versus normal weight, normal weight versus overweight, normal weight versus obese, and overweight versus obese. A p value of ≤ 0.05 was set as significant.

CHAPTER IV

RESULTS

Thirty percent of the subjects included in the data analysis were classified as normal weight, which is based on a BMI value of greater than or equal to 20 kg/m^2 and less than 25 kg/m^2. Only 1.7% of the subjects were classified as underweight, which is a BMI value of less than 18.5 kg/m^2. Thirty five and five-tenths percent of the subjects were classified as overweight, which is a BMI greater than or equal to 25 kg/m^2 but less than 30 kg/m^2, and 32.8% of the subjects were classified as obese, which is a BMI greater than or equal to 30 kg/m^2. Sixty-eight and three-tenths percent of the subjects were classified as either overweight or obese.

The underweight group had a lower are at screening compared with the normal weight group (Table 1). The overweight and obese groups were older at screening compared to the normal weight group. There was no difference between the overweight and obese group for age at screening.

The underweight group had lower waist circumference compared to the normal weight group (Table 1). The overweight group had a greater waist circumference than the normal weight group, and the obese group had a greater waist circumference compared to the normal weight group. The obese group had a greater waist circumference compared with the overweight group.

The underweight group had lower serum triglyceride levels compared to the normal weight group. Both the overweight and obese groups had greater serum triglycerides compared to the normal weight group, and the obese group had greater serum triglyceride levels compared to the overweight group (Table 2).

Table 1 Number of Subjects, Age at Screening, and Waist Circumference for Underweight, Normal Weight, Overweight and Obese Groups.

Group	Number of Subjects	Percentage of Subjects (%)	Age at Screening (Years)	Waist Circumference (cm)
Underweight	144	1.7	40.7 $\pm$ 1.6 *	69.6 $\pm$ 0.5 *
Normal Weight	2542	30.0	43.8 $\pm$ 0.4	82.0 $\pm$ 0.2
Overweight	3014	35.5	47.5 $\pm$ 0.4 **	95.7 $\pm$ 0.2 **
Obese	2785	32.8	47.4 $\pm$ 0.5 †	111.5 $\pm$ 0.4 †‡

Note: Using body mass index (BMI), subjects were classified at underweight (< 18.5 kg/m^2), normal weight (≥ 18.5 kg/m^2, < 25 kg/m^2), overweight(≥ 25 kg/m^2, < 30 kg/m^2), and obese (≥ 30 kg/m^2). Data for age at screening and waist circumference are presented as mean $\pm$ standard error of the mean

* $p < 0.001$, underweight vs. normal weight
** $p < 0.001$, overweight vs. normal weight
† $p < 0.001$, obese vs. normal weight
‡ $p < 0.001$, obese vs. overweight

The underweight group had lower serum total cholesterol levels than the normal weight group (Table 2). The overweight group and obese group had greater serum total cholesterol levels than the normal weight group. There was no difference between the overweight and obese groups for serum total cholesterol.

The underweight group had greater serum high density lipoprotein cholesterol (HDL-C) levels than the normal weight group (Table 2). Both the overweight and obese groups had lower serum HDL-C levels than the normal weight group. The obese group had lower HDL-C levels compared to the overweight group.

Table 2. Serum Triglycerides, Serum Total and High Density Lipoprotein Cholesterol, and Serum Glucose for Underweight, Normal Weight, Overweight and Obese Groups.

Group	Triglycerides (mmol/L)	Total Cholesterol (mmol/L)	High Density Lipoprotein Cholesterol (mmol/L)	Glucose (mmol/L)
Underweight	1.03 ± 0.07 **	4.53 ± 0.10 †	1.56 ± 0.04 *	4.76 ± 0.04 †
Normal Weight	1.24 ± 0.03	4.96 ± 0.03	1.48 ± 0.01	5.00 ± 0.04
Overweight	1.78 ± 0.05 ††	5.27 ± 0.03 ††	1.28 ± 0.01 ††	5.30 ± 0.03 ††
Obese	1.96 ± 0.05 ‡#	5.24 ± 0.03 ‡	1.19 ± 0.01 ‡$	5.53 ± 0.04 ‡$

Note: Using body mass index (BMI), subjects were classified at underweight (< 18.5 kg/m2), normal weight (> 18.5 kg/m2, < 25 kg/m2), overweight (> 25 kg/m2, < 30 kg/m2), and obese (> 30 kg/m2).

Data are mean ± standard error of the mean.

* $p < 0.05$, underweight vs. normal weight
** $p < 0.01$, underweight vs. normal weight
† $p < 0.001$, underweight vs. normal weight
†† $p < 0.001$, overweight vs. normal weight
‡ $p < 0.001$, obese vs. normal weight
# $p < 0.01$, obese vs. overweight
$ < 0.001 obese vs. overweight

The underweight group had lower serum glucose levels than the normal weight group (Table 2). The overweight and obese groups had greater serum glucose levels compared to the normal weight group. The obese group had greater serum glucose levels compared to the overweight group.

Chi-square analysis showed significant differences for the percentage of participants in each group who reported performing vigorous physical activity during the prior 30 days. Thirty-three and eight-tenths percent of participants in the normal weight group reported engaging in vigorous physical activity within the last 30 days. Only 24.3% of the participants in the underweight group reported performing physical activity within the prior 30 days. In the overweight group, 31.8% of the participants reported engaging in vigorous physical activity, which is similar to the normal weight group. Only 25.7% of the participants in the obese group reported doing vigorous physical activity during the last 30 days.

Table 3 Percentage of Participants Who Reported Participation in Vigorous Physical Activity Over the Past 30 Days and Estimated Cardiorespiratory Fitness (VO2max) for Underweight, Normal Weight, Overweight and Obese Groups.

Group	Participants Reporting Vigorous Physical Activity, Last 30 Days (%)	Estimated VO_2max (ml/kg/min)
Underweight	24.3	41.0 $\pm$ 1.8
Normal Weight	33.8 *	41.5 $\pm$ 0.4
Overweight	31.8	40.1 $\pm$ 0.6
Obese	25.7	38.3 $\pm$ 0.5 * **

Note: Using body mass index (BMI), subjects were classified at underweight (< 18.5 kg/m2), normal weight (> 18.5 kg/m2, < 25 kg/m2), overweight (> 25 kg/m2, < 30 kg/m2), and obese (> 30 kg/m2). Estimated VO2max was determined using a two-stage submaximal exercise test.

Data for participants reporting vigorous physical activity over the last 30 days are expressed as a percentage of the subjects for each BMI classification.
* $p < 0.001$, obese vs. normal weight.

Data for estimated VO_2max are mean $\pm$ standard error of the mean.
* $p < 0.001$, obese vs. normal weight
** $p < 0.001$, obese vs. overweight.

There was no difference between the underweight and normal weight groups for estimated VO_2max (Table 3). Also, there was no difference between the overweight and normal weight groups for VO_2max. The obese group had a lower estimated VO_2max value compared to the normal weight and overweight groups.

The underweight group was not different from the normal weight group for serum CRP level (Table 4). The overweight group and the obese group had greater CRP levels

than the normal weight group, and the obese group had a greater CPR level than the overweight group.

The underweight and normal weight groups were not different for serum homocysteine levels (Table 4). The overweight group had greater homocysteine levels compared to the normal weight group. The homocysteine level for the obese group was not different compared with the homocysteine levels for the normal weight and overweight groups.

There was no difference for the underweight and normal weight groups with respect to the age at which they were told that they had CHD (Table 4). Both the overweight and obese groups were at a younger age when informed that they had CHD compared to the normal weight group. There was no difference between the obese and overweight groups with respect to the age at which they were told that they had CHD.

Table 4 Inflammatory Markers, and Age When the Individual Was Informed that They Had Coronary Heart Disease (CHD) for Underweight, Normal Weight, Overweight and Obese Groups.

Group	C-Reactive Protein (mg/dL)	Homocysteine (umol/L)	Age when told had CHD (years)
Underweight	0.20 ± 0.04	8.03 ± 0.18	57.5 ± 9.0
Normal Weight	0.27 ± 0.01	8.26 ± 0.08	59.7 ± 1.9
Overweight	0.38 ± 0.02 †	8.57 ± 0.08 **	55.5 ± 1.4 *
Obese	0.62 ± 0.02 ‡ #	8.47 ± 0.11	52.6 ± 1.6 ††

Note: Using body mass index (BMI), subjects were classified at underweight (< 18.5 kg/m2), normal weight (> 18.5 kg/m2, < 25 kg/m2), overweight (> 25 kg/m2, < 30 kg/m2), and obese (> 30 kg/m2).

Data are mean ± standard error of the mean.

* $p < 0.05$, overweight vs. normal weight
**$p < 0.01$, overweight vs. normal weight
† $p < 0.001$, overweight vs. normal weight
††$p< 0.01$, obese vs. normal weight
‡ $p < 0.001$, obese vs. normal weight
# $p< 0.001$, obese vs. overweight

Dietary folic acid intake was not different between the underweight and normal weight groups. The overweight and normal weight groups did not differ for dietary folic acid intake. The obese group has a significantly lower dietary folic acid consumption compared to the normal weight group, but was not different compared with the overweight group.

Serum folate levels were not different between the underweight and normal weight groups or between the overweight and normal weight groups. Serum folate was lower in the obese group compared to the normal weight and overweight groups.

Table 5. Homocysteine, Dietary Folic Acid and Serum Folate for Participants Classified as for Underweight, Normal Weight, Overweight and Obese Groups.

Group	Homocysteine (μmol/L)	Dietary Folic Acid (μg)	Serum Folate (nmol/L)
Underweight	8.03 ± 0.18	236.8 ± 52.6	34.0 ± 2.3
Normal Weight	8.26 ± 0.08	207.1 ± 8.7	35.4 ± 0.7
Overweight	8.57 ± 0.08 *	194.8 ± 6.4	34.6 ± 0.5
Obese	8.47 ± 0.11	181.0 ± 5.1 **	31.4 ± 0.6 **‡

Note: Using body mass index (BMI), subjects were classified at underweight (< 18.5 kg/m2), normal weight (> 18.5 kg/m2, < 25 kg/m2), overweight (> 25 kg/m2, < 30 kg/m2), and obese (> 30 kg/m2).

Data are mean ± standard error of the mean.

* $p < 0.01$, overweight vs. normal weight
** $p < 0.001$, obese vs. normal weight
‡ $p < 0.001$, obese vs. overweight

CHAPTER V

DISCUSSION

Using the data using the combined data sets from 1999-2000 and 2001-2002 NHANES, 32.8% of the participants were classified as overweight and 68.3% of the participants in were classified as either overweight or obese. Most reports on the prevalence of overweight and obesity have used NHANES so similar values for prevalence would be expected. Using data from the 2003 – 2004 NHANES data set, the calculated prevalence of obesity for adults, 20 years of age and older, was 32.2% (Ogden, Carroll, Curtin, McDowell, Tanak, & Flegal, 2006). This included an obesity prevalence of 31.1% for men and 33.2% for women. Data from 1999-2000 NHANES showed a prevalence of obesity of 30.5% and a prevalence of overweight of 64.5% (Flegal.,Carroll, Ogden, & Johnson, 2002).

Multiple factors have contributed to the dramatic rise in the prevalence of overweight and obesity in the United States. These factors include social, economic and cultural changes over the prior century. Since body weight is determined by energy balance, the balance between calories consumed and calories expended determines whether body weight is decreased, maintained, or increased. Physical activity is a major determinant of energy expenditure; therefore, declining participation in physical activity

is recognized as a key contributing factor to the high prevalence of overweight and obesity.

In general, the major finding of the present study was that overweight and obesity were associated with a poor serum lipid profile, higher serum glucose levels, lower participation in physical activity and a lower physical fitness level, elevated serum levels of inflammatory markers for CVD, and a younger age at which participants were informed that they had CAD. Using survey data, it is not possible to determine the exact cause of the younger age at which overweight and obese participants were told that they had CAD, but physical activity levels and increased body fatness are both likely to be contributing factors as discussed below. Additionally, some of the effects of physical activity in improving serum lipid and glucose levels and even possible markers for inflammation may be mediated in part by the effect of physical activity in maintaining a lower body weight.

The poor serum lipid profile of the overweight and obese individuals included elevated serum triglycerides and total cholesterol and lower HDL-C compared with the normal weight group. This is consistent with the reported association of higher total cholesterol levels and reduced HDL-C in overweight and obese individuals, which are partially reversed by weight loss (Pasanisi, Contaldo, De Simone, & Mancini, 2001; Poirier & Despres, 2001). The blood lipid profiles of the overweight and obese groups was related to participants being told at a younger age that they had CAD, and it also is consistent with an increased risk for CVD (Anderson et al., 1987; Benfante & Reed, 1990; Huxley et al., 2002; Martin et al., 1986). The obese group in the present study had

a lower participation rate in physical activity also. Physical activity improves blood lipid profiles (Poirier & Despres, 2001). The obese group may have elevated serum total cholesterol and reduced HDL-C due to increased body weight and lower physical activity levels. Finally, there is a close relationship between physical activity, overweight and obesity, cholesterol levels and risk for CHD (Garrison et al., 1980).

The elevated blood glucose levels in the overweight and obese individuals are consistent with the decline in insulin insensitivity and reduced glucose uptake that accompany increased body fatness (Reaven, 2005). Higher blood glucose levels are an indicator of impaired glucose tolerance or increased resistance to insulin. Elevated blood glucose had been linked to an increased risk of CVD (Bowman & Armitage, 2002: Petersen & McGuire, 2005; Schnell, 2005). For example, CVD is a major cause of the reduction in life expectancy in patients with diabetes (Schnell, 2005). Seventy-five percent of diabetic patients die prematurely of cardiovascular complications. Both pre-diabetes and diabetes highly pre-dispose to cardiovascular alterations, and even serum glucose levels at the upper end of the normal range may predispose individuals to an increased risk of CVD (Schnell, 2005). Furthermore, elevated serum glucose levels have been linked with low grade inflammation (Barzilay & Freedland, 2003).

In the present study, one-third of the normal weight participants reported engaging in vigorous physical activity within the last 30 days. The rate of participation in vigorous physical activity was 31.8% in the overweight individuals, which is similar to that for the normal weight individuals. However, only one-fourth of the obese participants reported performing vigorous physical activity. Since physical activity is an

important component of a healthy lifestyle that includes weight maintenance or weight loss it is not surprising that a lower proportion of participants in the obese group reported participation in vigorous physical activity. The lack of difference between the normal weight and overweight groups was unexpected; however, the nature of this general question may not differentiate well between the actual amount and intensity of physical activity in which the participants in the various groups engaged.

Also in the present study, only the obese group had a lower physical fitness level compared with the normal weight group based on estimated VO_2max. This is consistent with the lower percentage of obese individuals reporting engaging in vigorous physical activity. It is worth noting that the overweight group had similar VO_2max values compared with the normal weight group. One might expect that as a group, cardiorespiratory fitness would be decreased to at least a small degree in the overweight participants. This lack of difference may be due to the test used. In NHANES, VO_2max was assessed using a submaximal two-stage exercise test rather than an incremental exercise test to maximum oxygen uptake. An exercise test to obtain an accurate maximum oxygen consumption is time consuming and would not be feasible when collecting data on large numbers of people. Also, there is an increased risk of adverse cardiovascular events during maximal exercise tests in men over 40 years of age and women greater than 50 years of age. However, the two-stage, submaximal test used in NHANES could have resulted in an increased measurement error. Also, there was little numerical difference for the estimated VO_2max between the groups. The numerical difference between the normal weight and obese groups was 3.2 ml/kg/min. Although

this was a statistically significant difference, the absolute difference was rather small. Also, the estimated VO_2max values for the groups appear to be slightly higher than published norms (American College of Sports Medicine, 2000).

From the present results, it can be concluded that there is a slight relationship between BMI and cardiorespiratory fitness. The extent to which elevated BMI or reduced cardiorespiratory fitness and lower physical activity participation contributed to the lower age at which participants in the obese group were informed that they had CAD cannot be determined from the present data. Many studies have reported a link between moderate and high levels of physical activity or increased physical fitness and a decreased risk of CVD and mortality due to CVD. Studies have demonstrated that higher levels of regular physical activity (Anderson, et al, 1997, Leon et al., 1987) and cardiorespiratory fitness (Lakka, et al., 1994) are associated with a reduced risk of CVD. Good cardiorespiratory fitness was shown to be associated with slower progression of early atherosclerosis in middle-aged men (Lakka et al., 2001). The relative risk of myocardial infarction for study participants in the upper third for maximal oxygen uptake (> 2.7 liters per minute) was 0.26 after adjustment for age and other variables as compared with the participants in the lowest third of VO_2max (Lakka et al., 1994). Higher levels of both leisure-time physical activity and cardiorespiratory fitness show strong, graded, inverse relationships with the risk of acute myocardial infarction (Lakka et al., 1994). The present results for participation in physical activity, cardiorespiratory fitness and being informed of having CAD are consistent with the published literature showing that increasing physical activity and improved physical fitness is related to a reduced incidence of CVD.

The results of the present study are consistent with studies that have reported that inflammatory markers, such as CRP and homocysteine, are elevated in overweight and obese individuals (Tamakoshi et al., 2002; Thorand et al., 2006). Findings from King et al. (2003) and Tamakoshi et al. (2002) suggest that being overweight or obese increases CRP levels, thus increasing the likelihood of CVD. Of the two inflammatory markers examined in the present study, the differences between groups were the most dramatic for serum CRP levels. Serum CRP levels were lowest in subjects categorized as underweight or normal weight. Serum CRP levels were 41% greater in the overweight subjects compared to subjects of normal weight. In obese individuals, CRP levels were 130% greater than in normal weight subjects and 63% greater in obese subjects compared with overweight subjects. Homocysteine levels also were greater in overweight and obese individuals compared to subjects who were underweight or normal weight; however the between group differences were not as dramatic as the between group differences for CRP. Using 2,258 non-Hispanic Whites, 1,856 non-Hispanic Blacks, and 1,584 Mexican-American participants drawn from the NHANES database, there was a negative association between serum homocysteine and BMI in non-Hispanic blacks and Mexican-Americans but not in non-Hispanic whites (Ganji & Kafai, 2004). In the present study, participants were not divided into groups based on race or ethnicity. The more dramatic relationship between CRP and body weight category compared with homocysteine and body weight category suggests that body weight may have a more dramatic effect on CRP levels than homocysteine. A population-based, cross-sectional study using data from NHANES from 1999 to 2002 examined a total of 1,444 adults between the ages of 20 to

49 years (Kuo et al., 2005). There was significant, inverse relationship between estimated VO_2max and homocysteine levels in women, but there was no relationship in men (Kuo et al., 2005). These data suggest that physical activity may effect homocysteine levels, at least in females. In summary, these results are consistent with recent reports of a link between increased body fatness and low-grade inflammation. Also, increased adiposity, especially increased amounts of visceral fat, as evidenced by increased values for BMI are related to greater risk for CVD. Both lack of physical activity and increased adiposity appear to be linked to increased systemic inflammation.

As would be expected subjects who were either overweight or obese were informed at a younger age that they had CAD compared to subjects who were underweight or normal weight. Subjects in the overweight group were 4.2 years younger than subjects in the normal weight group when informed that they had CHD, and subjects in the obese group were 7.1 years younger. These data are consistent with studies reporting an increased risk of CVD or CHD in individuals who are overweight and obese (Haapanen et al., 1997; Rodriguez et al., 1994).

Dietary folic acid intake and serum folate levels have strong, inverse relationships with serum homocysteine levels (Ganji and Kafai, 2004). For example, homocysteine concentrations in young women, aged 25 to 30 years, and in 288 older women, aged 60 to 65 years, were inversely related to total folate consumption and folic acid intake from supplements (Rasmussen et al., 2000). Using data from the third NHANES, 1988-1994, serum folate was reported to be a strong determinant of homocysteine levels (Ganji and Kafai, 2004). In the present study, dietary folic acid and serum folate levels cannot

explain the higher homocysteine levels in the overweight group compared to the normal weight group. The overweight group had significantly higher homocysteine levels, even though there dietary folic acid consumption and serum folate were not different compared to the normal weight group. Dietary folic acid intake and serum folate levels were significantly lower only in the obese group compared to the normal weight group, but the homocysteine levels were not significantly different compared to the normal weight group. Dietary folic acid intake and serum folate levels cannot explain the results for homocysteine levels in this study, suggesting that BMI or physical activity do effect homocysteine levels..

Summary and Conclusion

The purpose of this study was to determine the relationship between BMI and physical fitness, blood lipids, and inflammatory markers, as well as the relationship of these variables to CVD using the National Health and Nutrition Examination Survey (NHANES) 1999 - 2002 database. Our results support the research hypotheses: 1) individuals who were normal weight based on BMI classification had higher levels of physical fitness compared to obese individuals; 2) individuals who were normal weight had lower serum triglyceride and total cholesterol levels compared with overweight and obese individuals; 3) individuals who were normal weight had lower serum glucose levels compared with overweight and obese individuals; 4) individuals who were normal weight had lower serum levels of CRP compared to the overweight and obese individuals, as well as lower levels of homocysteine compared with the overweight group; and, 5) individuals who were in the normal weight group had a greater age when

they were told that they had CHD compared with overweight and obese individuals. In summary, the results of the present study show that overweight and obesity were associated with a poor serum lipid profile, higher serum glucose levels, lower participation in physical activity and a lower physical fitness level, elevated serum levels of inflammatory markers for CVD, and a younger age at which participants were informed that they had CAD.

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