OBESITY, PHYSICAL ACTIVITY AND INFLAMMATION: EXAMINING THE DEVELOPMENT OF ISCHEMIC HEART DISEASE AMONG NOVA SCOTIANS

by

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Abstract

Background: CVD is a major cause of premature death in Nova Scotia, Canada. **Objective:** To determine the role of inflammation in the relationships between obesity, physical activity and IHD. **Methods:** Secondary analysis using exposure data from the 1995 Nova Scotia Health Survey, morbidity data from CIHI and mortality data from Statistics Canada. **Results:** A statistically significant association was found between abdominal obesity and IHD for women; the relationship between physical inactivity and IHD was of borderline statistical significance in men. Inflammatory markers were independently associated IHD for women. **Conclusions:** Abdominal obesity was a risk factor for IHD for women, whereas physical inactivity was the was the strongest predictor of IHD in men. Inflammation was found to be an independent risk factor for IHD in women but not men. There was no evidence that inflammation plays a mediating role in the obesity-IHD and physical activity-IHD relationships for women and men, respectively.

List Of Abbreviations And Symbols Used

BMI	Body Mass Index
CIHI	Canadian Institute for Health Information
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
HDL	High-density Lipoprotein
HR	Hazard Ratio
ICAM	Intercellular Adhesion Molecule
ICD	International Classification of Diseases
IHD	Ischemic Heart Disease
IL-6	Interleukin 6
IQR	Interquartile Range
LDL	Low-density Lipoprotein
N	Number
NS	Not significant
NSHS	Nova Scotia Health Survey
RR	Relative Risk
SD	Standard Deviation

Chapter 1

Introduction

Cardiovascular disease (CVD) is one of the most important health issues affecting the Canadian population. The Public Health Agency of Canada (2007) has identified chronic diseases such as CVD as priority areas for health intervention. Diseases of the cardiovascular system, including myocardial infarction, ischemic heart disease (IHD), valvular heart disease, peripheral vascular disease, arrhythmias and stroke, are the cause of one out of every three Canadian deaths (Statistics Canada, 2010). Ischemic heart disease, which includes myocardial infarction, angina pectoris and atherosclerosis, makes up the largest proportion of CVD deaths (Statistics Canada, 2010).

Cardiovascular disease places a significant economic burden on the Canadian healthcare system. Although some individuals die unexpectedly from cardiovascular events without prior diagnosis, CVD is often chronic and people may live with it for years after diagnosis. Monitoring and treatment for these individuals includes visits with family physicians or cardiologists, diagnostic tests, medications, emergency room visits, hospitalizations and surgeries, all of which result in significant healthcare costs. For example, one estimate for the average annual hospitalization cost for an individual in Canada with coronary artery disease was $1743 (Smolderen et al, 2010).

The burden of CVD in Canada also includes the personal costs for individuals living with the disease. Evidence shows that individuals with coronary artery disease score significantly lower on measures of health-related quality of life than those without this disease (Xie et al, 2008). Given that 1.29 million Canadians reported having heart

disease in 2005 (Lee et al, 2009), this disease is clearly having a significant effect on the population.

Many CVD risk factors have been identified, including physical inactivity, smoking, obesity, diabetes and hyptertension (Public Health Agency of Canada, 2009). Data collected from the Canadian Community Health Survey between 1994 and 2005 indicates that rates of obesity, diabetes and hypertension have increased significantly in the Canadian population during this period (Lee et al, 2009). Other risk factors include age, gender, ethnicity, family history, dyslipidemia, excessive alcohol use and stress (Public Health Agency of Canada, 2009). The modifiable risk factors warrant special study, as they may be targeted through clinical or public health interventions to decrease the morbidity and mortality from CVD.

Recently, inflammation has been identified as another potentially important predictor of cardiovascular risk (Panagiotakos et al, 2008; Buckley et al, 2009), and has been etiologically linked to both obesity (Pitsavos et al, 2007; Wee et al, 2008; Compher & Badellino, 2008; Agrawal et al, 2009) and physical inactivity (Pitsavos et al, 2007, Arikawa et al, 2010). Elevated levels of specific inflammatory markers, such as C-reactive protein (CRP), have been associated with a higher risk of experiencing an incident fatal or nonfatal myocardial infarction (Cushman et al, 2005). After an acute cardiovascular event has occurred, these markers have also been shown to predict the risk of experiencing a recurrent event (Marcinkowski et al, 2007). However, the specific mechanisms in the relationships between inflammation, obesity, physical activity and CVD are unclear.

When compared to national rates, CVD and obesity disproportionately affect

Atlantic Canadians, and are major contributors to morbidity and mortality in this population (Statistics Canada, 2010). This retrospective cohort study used health information from Nova Scotians to analyze the relationship between physical activity, excess body weight, inflammation and IHD. It was conducted as a secondary analysis of data previously compiled by Dr. Karina Davidson and colleagues to study the relationship between depression, inflammation and CVD (Davidson et al, 2009).

The following literature review will examine and summarize some of the current publications in the areas of obesity, physical activity, inflammation and CVD. Standard methods of measuring these variables will also be addressed.

Chapter 2

Literature Review

2.1 Obesity and Cardiovascular Disease

According to data from the Canadian Community Health Survey, an estimated 61.9% of the Canadian adult population was overweight or obese in 2008 (Statistics Canada, 2010). When compared to the Canadian obesity rate of 14% in 1978-9 (Tjepkema, 2005), it is apparent that the prevalence of obesity is increasing steadily. Evidence suggests that this trend is occurring in all provinces and across socio-economic groups (Lee et al, 2009).

In Nova Scotia specifically, the rate of overweight and obesity is even higher: an estimated 63% of adults in this province had a self-reported BMI in the overweight or obese range in 2009 (Statistics Canada, 2010). In this province in 2007, CVD accounted for almost 2400 deaths, 1200 of which were attributed to IHD (Statistics Canada, 2010).

Excess body fat can be viewed as both an adverse health condition in itself and as a risk factor for other diseases. It has been associated with the development of CVD, type II diabetes, sleep apnea, osteoarthritis and certain types of cancer. Obesity is also related to other risk conditions, including dyslipidemia and hypertension (Heart and Stroke Foundation of Canada, 2006).

The presence or absence of excess body fat is one of the most important factors affecting an individual's risk of developing CVD (Hubert et al, 1983; Welborn et al, 2003; Yusuf et al, 2005; Li et al, 2006; Pardo Silva et al, 2006; Nusselder et al, 2009; Baena-Diez et al, 2010; Arnlov et al, 2010; Sehested et al, 2010). The Framingham Heart Study was among the first to identify the importance of this risk factor. It followed a

cohort of 5070 adults prospectively from 1948 and found that obesity made a significant contribution to CVD risk independently of other obesity-related CVD risk factors, such as diet, physical activity and diabetes (Hubert et al, 1983). Numerous other studies have since replicated these results, reporting a relative risk of CVD due to obesity of between 1.33 and 5.9 (Welborn et al, 2003; Yusuf et al, 2005; Pardo Silva et al, 2006; Nusselder et al, 2009; Arnlov et al, 2010; Sehested et al, 2010). The relationship has been demonstrated in both sexes, among younger and older adults, and across a variety of ethnic groups (Yusuf et al, 2005). Results from key studies addressing the relationship between fat and CVD are summarized in Table 1.

The Nurses' Health Study, another important epidemiological study, gathered data from 121 000 female nurses beginning in 1976 and continuing biennially thereafter. Results indicated that weight change during adulthood, as compared to self-reported weight at age 18, was significantly associated with increased risk of coronary heart disease. Women who gained between 4 and 10 kg during adulthood had a 27% higher risk (RR = 1.27, 95% CI 1.12 - 1.45) of coronary heart disease compared to those whose weight changed less than 4 kg (Li et al, 2006). Among women who gained greater than 40 kg, the relative risk of coronary heart disease due to weight gain was 3.86 (95% CI 3.02 - 4.94) (Li et al, 2006).

The magnitude of the relationship between obesity and CVD varies according to which obesity measurement tool is used; several methods have been developed. Body weight alone is considered to be of limited usefulness because the range of healthy body weights for an individual varies greatly according to his or her height. Perhaps the most commonly used measure of obesity is the Body Mass Index (BMI), which is a tool used

Table 1 - Summary of studies examining the relationship between obesity and CVD

Authors and Year	Design	Study population	Obesity and CVD Measure	Main Findings (Adjusted RR or HR)	Adjusted for
Welborn et al, 2003	Prospective cohort	9206 M, F Age 20-69 Australian Risk Factor Prevalence Survey	BMI WC WHR CHD mortality	M: WHR: **1.47** (1.10 – 1.96) F: WHR: **1.88** (1.26 – 2.81)	BMI, WC, BP, cholesterol, LDL,HDL, triglycerides, smoking, diabetes
Yusuf et al 2005	Case-control	27098 M, F 52 countries Cases - first MI presenting within 24 hours of symptom onset Controls - attendant of non-cardiac patient	BMI WC HC WHR MI	BMI: 0.98 (95% CI 0.88-1.09) WC: **1.33** (1.16-1.53) WHR: **1.75** (1.57-1.95)	Smoking, Apo B/Apo A ratio, hypertension, diabetes mellitus, diet, activity, alcohol, psychosocial variables
Pardo Silva et al 2006	Retrospective cohort	2251 M,F Age 45 Part of Framingham Heart Study	BMI CVD MI mortality	Incidence M: CVD: **2.19** (95% CI 1.36-3.52) M: MI: **2.04** (1.09-3.84) F: CVD: 1.27 (0.07-22.66) F: MI: 1.03 (0.32-3.31)	Smoking status, number of cigarettes smoked/day, hypertension, diabetes mellitus, serum cholesterol
Arnlov et al 2010	Population-based prospective cohort	1758 M Age >50 years Follow-up: median 30 years	BMI Major CVD event	BMI >30 compared to BMI <25: **1.95** (1.14-3.34)	Age, smoking status, LDL cholesterol

Table 1 - Summary of studies examining the relationship between obesity and CVD (continued)

Authors and Year	Design	Study population	Obesity and CVD Measure	Main Findings (Adjusted RR)	Adjusted for
Baena-Diez et al 2010	Population-based prospective cohort	932 M, F Age 35-84 Follow-up: 10 years	BMI Heart failure	BMI >30 compared to BMI <25: **2.45** (1.02-5.61)	Age, sex, HTN, IHD, diabetes
Sehested et al, 2010	Prospective cohort	2493 M, F Age 41-72 No history of CVD	BMI WC HC WHR Incident CVD (CVD death, MI, stroke)	M: WHR: 1.06 (95% CI 0.64 – 1.77) F: WHR: 1.31 (95% CI 0.69 – 2.48)	Diabetes, dyslipidemia, hypertension, hyper-insulinemia, inflammatory markers

BMI – body mass index
CHD – coronary heart disease
CHF – congestive heart failure
CVA – cerebrovascular accident
HC – hip circumference
IHD – ischemic heart disease
MI – myocardial infarction
WC – waist circumference
WHR – waist to hip ratio

to assess weight while controlling for height. In this way, it allows objective comparisons of the weights of individuals of different heights. It is calculated by dividing an individual's weight by the square of his or her height, and is therefore measured in units of kg/m^2. Health Canada's BMI classifications, as taken from their 2003 document Canadian Guidelines for Body Weight Classifications, are outlined in Table 2.

Table 2 - Health Canada body weight classification system according to BMI (2003)

BMI level (kg/m^2)	**Classification**
<18.5	Underweight
18.5 - 24.9	Normal weight
25.0 - 29.9	Overweight
30.0 and over	Obese
30.0 - 34.9	Obese Class I
35.0 - 39.9	Obese Class II
≥ 40.0	Obese Class III

However, some evidence suggests that BMI is not accurate in assessing obesity or adiposity in all individuals, specifically because of its inability to distinguish between adipose tissue and lean muscle mass. As part of the National Health and Nutrition Examination Survey, both BMI and body fat percent were measured in 13 601 adults, and the correlation between the measurements was assessed. Using BMI measurements to define obesity resulted in 19% of the men and 24% of the women being classed as obese, while using body fat percent resulted in 44% of the men and 52% of the women being classed as obese (Romero-Corral et al, 2008). Body mass index as a tool to detect body fat percent-defined obesity had a high specificity (95% in men, 99% in women) but a low sensitivity (36% in men, 49% in women) (Romero-Corral et al, 2008). Therefore, most of the people classified as obese using BMI were obese according to body fat percent, but

there were a considerable number of people who were obese according to body fat percent but whom the BMI failed to capture.

Body mass index has also been criticized for its inability to account for distribution of body fat. Abdominal obesity specifically has been associated with greater cardiovascular health risk than overall obesity (Welborn et al, 2003; Yusuf et al, 2005; Price et al, 2006; Winter et al, 2008; Sehested et al, 2010), and for this reason, waist circumference and waist-to-hip ratio are often used instead of, or in addition to, BMI. Because of the differing body proportions between men and women, sex-specific cut-off points have been determined. Males are considered to have an increased risk of abdominal obesity-related outcomes if their waist circumference is greater than or equal to 102 cm, while the cut-off point for females is greater than or equal to 88 cm (Health Canada, 2003). Similarly, males are considered to have increased risk if their waist-to-hip ratio is greater than or equal to 1.0, and females if their waist-to-hip ratio is greater than or equal to 0.85 (World Health Organization, 2000).

The relationship between obesity and CVD has also been demonstrated for specific cardiovascular outcomes. Obesity is associated with an increased risk of chronic heart failure (Baena-Diez et al, 2010), stroke (Winter et al, 2008) and CVD-related mortality (Price et al, 2006).

Individuals with obesity experience a lower life expectancy, and can expect fewer CVD-free years, than their normal weight counterparts. Using information from the Framingham Heart Study, age of CVD development, length of time affected by CVD, and life expectancy was determined in 5209 subjects. Results showed that, on average, overweight individuals had lower total life expectancy than normal weight individuals

(1.3 years for males and 1.0 years for females). Differences were also seen in CVD-free years, with overweight individuals being diagnosed with CVD earlier than their normal weight counterparts (3.1 years for males and 2.9 years for females) (Nusselder et al, 2009). For this reason, overweight and obese individuals tended to have more years of living with CVD.

2.2 Physical Activity and Cardiovascular Disease

Physical inactivity has been identified as an important risk factor for CVD (Mora et al, 2007; Nocon et al, 2008; Sofi et al, 2008; Kodoma et al, 2009). An inverse, linear dose-response relationship has been established between the amount of physical activity and CVD incidence and mortality (Haennel & Lemore, 2002; Sofi et al, 2008), and also between level of physical fitness and risk of CVD events (Kodoma et al, 2009). The term physical activity refers to behaviour that expends calories, while physical fitness refers to a physiological state that can be influenced by participation in physical activity, as well as other factors such as genetic predisposition. Thus, while physical fitness and physical activity are two separate but highly related concepts, they are often studied together to gain a better understanding of the relationship with CVD. For this reason, for the purpose of this literature review, studies examining these topics will be summarized together.

The relationship between physical activity and CVD mortality is well established, as seen in the studies outlined in Table 3. A recent meta-analysis examining data from 883 373 subjects in 33 cohort studies determined that a high level of physical activity or fitness was associated with a relative risk of cardiovascular mortality of 0.65 (95% CI 0.60 - 0.70) (Nocon et al, 2008). Other large meta-analyses have reached very similar conclusions, suggesting a relative risk of cardiovascular disease due to a high level of physical fitness and/or physical activity of 0.64-0.73 (Hamer & Chida, 2007; Sofi et al, 2008; Kodoma et al, 2009).

Participation in physical activity has also been associated with various CVD risk factors. For example, one study found that 59% of the reduction in CVD attributed to

physical activity was actually occurring through the mediating effects of other risk factors; specifically inflammatory markers, blood pressure, blood lipids and BMI (Mora et al, 2007). Increased amounts of physical activity have also been significantly associated with other CVD risk factors, including lower levels of weight, waist circumference, diastolic blood pressure, total cholesterol, low-density lipoproteins and triglycerides (Aadahl et al, 2009).

There have been conflicting recommendations regarding the frequency, duration and intensity of exercise needed to decrease the risk of poor cardiovascular outcomes. A review of the literature determined that an energy expenditure of approximately 1000 kilocalories (4200 kilojoules) per week is likely sufficient to result in a protective effect against CVD development (Haennel & Lemire, 2002). A more recent review of the literature also reached this conclusion (Warburton et al, 2008). In an average individual that spends 60 calories per kilometer, approximately 1000 kilocalories could be expended by walking 125 city blocks, or 16km. With a walking speed of 6km/hour, the expenditure of 1000 kilocalories per week would be similar to the current Canadian guidelines for physical activity, which suggest that adults participate in at least 30 minutes of moderate physical activity, for example, walking briskly, most days of the week (Haennel & Lemire, 2002). More recent American guidelines are comparable, recommending that adults participate in moderate-intensity activity for at least 30 min per day, five days per week, or vigorous-intensity for at least 20 minutes, three days per week (Haskell et al, 2007).

The Canadian guidelines are currently under review, with the proposed new guidelines identifying a target of 150 minutes per week of moderate physical activity. An

analysis of accelerometer data from the 2007-2009 Canadian Health Measures Survey recently concluded, however, that only 17% of Canadian men and 14% of Canadian women are meeting these new targets (Colley et al, 2011).

Physical activity can also be broadly classified as leisure-time, occupational, transportation and household chores (Armstrong & Bull, 2006). The two most frequently studied are leisure-time and occupational, both of which have been shown to influence CVD risk (Altieri et al, 2004; Probert et al, 2008; Sofi et al, 2008). Predictably, individuals who participate in the highest levels of both leisure-time and occupational physical activity demonstrate the greatest reduction in CVD risk (Probert et al, 2008).

Recently, there has been interest in evaluating the risks associated with lack of occupational physical activity, also known as occupational sitting. A systematic review of the literature concluded that while case-control studies did suggest a possible link between occupational sitting and BMI, the prospective studies were inconclusive (Van Uffelen et al, 2010). However, the prospective studies examined did suggest that occupational sitting was associated with risk of diabetes mellitus and all-cause mortality (Van Uffelen et al, 2010). High amounts of sitting time throughout the day have also been associated with increased risk of cardiovascular mortality (Katzmarzyk et al, 2009). The risks of occupational sitting are particularly concerning because data compiled from the National Population Health Surveys and Canadian Community Health Surveys show that while leisure- and transportation-related physical activity increased among Canadian adults between 1994 and 2005, occupational physical activity decreased significantly (Juneau & Potvin, 2010).

In the majority of studies, physical activity is assessed by asking the participants

about their frequency, duration and intensity of exercise. However, there are concerns with respect to the accuracy of information when assessing physical activity through self-report measures, with some evidence suggesting that individuals' estimations of their activity levels are often significantly higher or lower than their actual participation (Prince et al, 2008). Despite this, self-report is the accepted standard for measuring physical activity, and for a large sample size, self-report is the most practical method. Also, the use of self-reported physical activity has some value from a practical standpoint, as this is the method that clinicians would generally use to assess physical fitness and make recommendations to their patients. Some examples of physical activity assessment tools that use self-report data include the Global Physical Activity Questionnaire, the Baecke Physical Activity Questionnaire and the Paffenbarger Physical Activity Questionnaire (National Cancer Institute, 2010).

Table 3 - Summary of studies examining the relationship between physical activity and CVD

Authors and Year	Study design	Study Population	Physical activity and CVD measure	Main findings	Adjusted for
Altieri et al 2004	Case-control	Cases 507 Controls 478 M, F Hospital based Italy	First acute MI	ORs for acute MI by PA (most active to least active) OPA: differed by age between **0.51-0.61** (95% CIs significant) LTPA: NS	Age, sex, education, BMI, cholesterol, smoking, coffee, alcohol, diet, family history, diabetes, dyslipidemia,
Hamer & Chida 2007	Meta-analysis	18 prospective studies with 459 833 participants	Any of: self-reported walking time, distance, pace, energy expenditure CVD and all-cause mortality	Overall HR = 0.69 (95% CI 0.61-0.77)	Most studies adjusted for age, smoking, alcohol
Mora et al 2007	Prospective	27055 F Mean follow-up 10.9 years	Self-report PA (time per week spent on recreational activities, # flights of stairs daily) Incident CVD (MI, Ischemic stroke, CVD-related health interventions, CVD-related death), incident CHD	Compared to referent of <200kcal/wk >=1500kcal/wk HR **0.62** (0.52-0.75, p<0.001)	Age, treatment, smoking
Nocon et al 2008	Review & Meta-analysis	33 cohort studies with 883 373 subjects Minimum 5000 participants per study Follow-up 4-20 years	Self-report (24) or fitness test (9) CVD and all-cause mortality	Comparing highest PA vs. lowest PA RRs ranged from 0.19 - 0.89 Most between 0.30 - 0.50 Overall pooled RR = **0.65** (95% CI 0.60-0.70)	Most studies adjusted for high blood pressure, high cholesterol, obesity

Table 3 Summary of studies examining the relationship between physical activity and CVD (continued)

Authors and Year	Study design	Study Population	Physical activity and CVD measure	Main findings	Adjusted for
Probert et al 2008	Canadian Community Health Survey Cross-sectional	77 011 M, F Age 18-64 Representative of 98% of Canadian population	Self-report OPA and LTPA Metabolic Equivalents Self-report chronic condition or heart disease	ORs for heart disease by PA (Active compared to sedentary) OPA: **0.61** (95% CI 0.49-0.78) LTPA: NS	Sex, age, BMI, ethnicity, income, education, time since immigration, smoking
Sofi et al 2008	Meta-analysis of prospective cohort studies	26 studies with 513 472 subjects Follow-up 4-25 years	LTPA CHD	Highest PA vs. lowest PA: RR **0.73** (0.66-0.80) Moderate PA vs lowest PA: RR **0.88** (0.83-0.93)	Most adjusted for age, smoking, obesity, blood pressure, cholesterol
Kodoma et al 2009	Meta-analysis of cohort studies	33 studies with 84323 subjects	Maximal aerobic capacity expressed in metabolic equivalents CHD or CVD	Low fitness vs high fitness: **1.56** (1.39-1.75) Low fitness vs. intermediate fitness: **1.47** (1.35-1.61)	Most adjusted for sex, smoking, obesity, BP, cholesterol, diabetes.

CHD – coronary heart disease
CI – Confidence interval
CRP – C-reactive Protein
LTPA – Leisure-time physical activity
MI – myocardial infarction
NS – not significant
OPA – occupational physical activity
OR – odds ratio
PA – physical activity
RR – relative risk

2.3 Obesity, Physical Activity and Cardiovascular Disease

It is widely accepted that there are major adverse health outcomes related to obesity (Hubert et al, 1983; Welborn et al, 2003; Yusuf et al, 2005; Li et al, 2006; Pardo Silva et al, 2006; Nusselder et al, 2009; Baena-Diez et al, 2010; Arnlov et al, 2010; Sehested et al, 2010), and that physical activity can have significant health benefits (Altieri et al, 2004; Hamer & Chida, 2007; Mora et al, 2007; Nocon et al, 2008; Probert et al, 2008; Sofi et al, 2008; Kodoma et al, 2009). As seen in Table 3, several studies have also examined the interactions between physical activity and obesity. These studies demonstrated that the protective effects of exercise are present even among obese individuals (Church et al, 2005; Li et al, 2006; Sui et al, 2007; Wing et al, 2007; Orsini et al, 2008; Weinstein et al, 2008). Therefore, even as the proportions of overweight and obese individuals in society continue to increase, there are behaviors that can help to protect these individuals from adverse cardiovascular outcomes.

As seen in Table 4, studies examining the relationship between excess body weight, physical activity or fitness and CVD traditionally use individuals of normal weight and high activity or fitness level as the reference group. Normal weight individuals with moderate or low activity or fitness then have been shown to have a relative risk of CVD of between 1.3 and 2.7 (Church et al, 2005; Li et al, 2006; Orsini et al, 2008). Among overweight individuals, again comparing to the normal weight and high activity group, the relative risk of CVD for high activity or fitness level has been estimated at between 1.4 and 1.5 (Li et al, 2006; Weinstein et al, 2008). Statistically significant estimates of the relative risk of CVD for overweight individuals with moderate or low activity has been shown to lie between 1.4 and 2.7 (Church et al, 2005;

Table 4 - Summary of studies examining the relationship between obesity, physical activity and CVD

Authors and Year	Study Design	Study Population	Obesity, Physical activity and CVD measure	Main findings	Adjusted for
Church et al 2005	Prospective observational Aerobics Center Longitudinal Study	2316 M All have diabetes mellitus	BMI Maximal exercise test CVD mortality	Hazard ratios Normal weight: High fitness: 1.0 (ref), Mod fitness: **2.3** (95% CI 1.2-4.6), Low fitness: **2.7** (1.3-5.7) Overweight: High fitness: NS, Mod fitness: NS, Low fitness: **2.7** (1.4-5.1) Obese: High/moderate fitness: NS, Low fitness: **2.8** (1.4-5.6)	Age, examination year, fasting glucose, SBP, parental history of premature CVD, total cholesterol, smoking, abnormal resting ECG, abnormal exercise ECG
Li et al 2006	Longitudinal Nurses' Health Study	88 393 F Age 34-59 Follow-up 20 years	Self-report BMI WC HC WHR Self-report participation in moderate and vigorous activities Incident CHD events (nonfatal MI, fatal CHD)	Relative risks Normal weight: High PA: 1.0 (ref), Mod PA: **1.32** (95% CI 1.12-1.56), Low PA: **1.48** (1.24-1.77) Overweight: High PA: **1.43** (1.13-1.82), Mod PA: **1.92** (1.61-2.30), Low PA: **2.04** (1.67-2.48) Obese: High PA: **2.48** (1.84-3.34), Mod PA: **3.32** (2.74-4.01), Low PA: **3.44** (2.81-4.21)	Age, smoking status, parental history of CHD, menopausal status, hormone use, aspirin use, alcohol consumption
Sui et al 2007	Prospective cohort	2603 M,F Age 60 years and older Mean follow-up 12 years	BMI WC Body fat % Maximal exercise test All cause mortality	Fitness is a significant predictor of all-cause mortality, independent of BMI, WC, body fat percentage Low fitness greater risk for CHD than obesity	Smoking, baseline health

Table 4 - Summary of studies examining the relationship between obesity, physical activity and CVD (continued)

Authors, Year	Study Design	Study Population	Obesity, Physical activity and CVD measure	Main findings	Adjusted for
Wing et al 2007	Longitudinal Look AHEAD Study	5145 M,F Ethnically diverse Overweight/ obese Type II diabetes mellitus	BMI Maximal exercise test CVD risk factors: HTN, dyslipidemia, poor blood glucose control	Low fitness associated with: High Framingham risk score, high HbA1c (indicating poor blood glucose control) High fatness associated with: high systolic blood pressure	Age, smoking, diabetes duration, race
Orsini et al 2008	Prospective cohort	37 633 M Age 45-79 Follow-up 9.7 years	BMI Self-report occupational and leisure-time physical activity CVD-related mortality	Normal weight: High PA: 1.0 (ref), Medium PA: 0.99 (0.74-1.32), Low PA: **1.41** (1.07-1.86) Overweight: High PA: 1.05 (0.78-1.41), Medium PA: 1.04 (0.77-1.39), Low PA: **1.43** (1.09-1.88) Obese: High PA 1.44 (0.85-2.45), Medium PA **1.86** (1.20-2.87), Low PA: **1.94** (1.30-2.90)	Age, smoking, alcohol, educational level, parental history of CVD, cancer
Weinstein et al 2008	Prospective cohort Women's Health Study	38 987 F Mean follow-up 10.9 years	BMI Active if >1000kcal/week expended on recreational activities Incident CHD	Normal weight: Active: 1.0 (ref), Inactive: 1.08 (0.84-1.39) Overweight: Active: **1.54** (1.14-2.08), Inactive: **1.88** (1.46-2.42) Obese: Active: **1.87** (1.29-2.7), Inactive: **2.53** (1.94-3.30)	Age, Parental history of MI, Alcohol, Smoking, use of hormone therapy, dietary factors

BMI – Body Mass Index
CHD – congestive heart failure
ECG – electrocardiogram
HC – hip circumference
PA – physical activity
SBP – systolic blood pressure
WC – waist circumference
WHR – waist to hip ratio

Li et al, 2006; Orsini et al, 2008; Weinstein et al, 2008).

It is more difficult to study these relationships among obese individuals. Excess body weight and physical activity or fitness level have, themselves, been shown to be inversely correlated, such that there are relatively few individuals in the highest category of body weight who are in the highest physical activity category. However, the information available suggests that obese individuals who are in the highest activity group may have a relative risk of CVD of between 1.9 and 2.5 (Li et al, 2006; Weinstein et al, 2008), while those in the moderate or low activity groups may have a relative risk of CVD of between 1.9 and 3.4 (Church et al, 2005; Li et al, 2006; Orsini et al, 2008; Weinstein et al, 2008).

Because of the multiple obesity and physical activity categories examined in these studies, the overall patterns can be difficult to interpret. Therefore, Table 5 displays an overview of the results of the studies included in the literature. The differences in classification of high, moderate and low levels of physical activity between studies is clearly a limitation when comparing their results; however, the general trend seen in Table 4 suggests that CVD risk increases with higher body weights and lower physical activity or fitness.

Table 5 – Summary of results (expressed in Relative Risks or Hazard Ratios) of studies examining relationship between obesity, physical activity and CVD

	Physical activity or fitness		
Body weight		High	Moderate or low
	Lean	1.0 (referent)	1.3 – 2.7
	Overweight	1.4 – 1.5	1.4 – 2.7
	Obese	1.9 – 2.5	1.9 – 3.4

As with the relationship between physical activity and CVD risk outlined above, some of the association between obesity, physical activity and CVD may be due to mediating effects of other related factors. However, there is some evidence showing that obesity and physical activity are likely to each influence different cardiovascular risk factors (Wing et al, 2007). For example, physical fitness has been shown to have a significant association with blood glucose control and Framingham risk score, while excess body weight has been shown to be significantly associated with systolic blood pressure (Wing et al, 2007).

This topic is complex and rapidly evolving, and there is no decisive conclusion regarding which of obesity or physical fitness has the stronger influence on cardiovascular risk. Some evidence has even suggested that lean sedentary men are at higher risk of CVD mortality than overweight active men (Li et al, 2006). However, the majority of findings show that although increasing levels of physical activity or fitness do mitigate some of the risk, cardiovascular risk continues to increase with greater body mass (Church et al, 2005; Li et al, 2006; Sui et al, 2007; Orsini et al, 2008; Wing et al, 2007; Weinstein et al, 2008). In other words, overweight and obese individuals cannot "exercise away" their excess cardiovascular risk – even with high physical fitness they will still experience an excess risk due to their weight.

2.4 Inflammation and Cardiovascular Disease

In addition to the traditional cardiovascular risk factors such as diet, obesity, physical activity and serum cholesterol, inflammation is increasingly being recognized as a significant predictor of cardiovascular risk. Inflammation in the body can result from a variety of physical conditions, including infection (Agapakis et al, 2010), physical trauma such as surgery (Shen et al, 2009), and cancer (Prizment et al, 2011). A variety of inflammatory markers have been investigated in the literature, including C-Reactive Protein (CRP), Interleukin-6 (IL-6), fibrinogen and soluble intercellular adhesion molecule-1 (ICAM). There is mounting evidence of a relationship between elevated levels of inflammation and risk of CVD development (Panagiotakos et al, 2008; Buckley et al, 2009). The Cardiovascular Health Study was a longitudinal study examining various factors associated with the development of incident coronary heart disease among 3971 older adults. Participants were grouped by CRP level according to current practice guidelines of the American Heart Association, whereby CRP levels were divided into three levels of risk: less than 1.0 mg/L was considered low risk, 1.0 - 3.0 mg/L considered average risk, and greater than 3.0 mg/L classified as high risk (Pearson et al, 2003).

Results showed that the highest CRP levels tended to be associated with being female and black, as well as with the presence of obesity, aspirin use, low levels of high density lipoprotein, hypertension, diabetes and smoking. After adjusting for these variables, the highest CRP level of >3 mg/L was associated with a 45% increased risk of coronary heart disease (Cushman et al, 2005). The population attributable risk was also calculated and it was further determined that if the elevated CRP levels could be

corrected, up to 11% of the incident coronary heart disease in this age group could be eliminated (Cushman et al, 2005). Other studies have cited inflammation as one of the most important predictors of cardiovascular disease development (Panagiotakos et al, 2008).

Not only have inflammatory markers been shown to have predictive value regarding the risk of developing CVD, evidence suggests they may also have prognostic value once a cardiovascular event has already occurred (Den Hertog et al, 2009). In a study of outcomes after ischemic stroke, blood samples were taken within 12 hours of symptom onset and CRP levels were analyzed. Patients with high levels of CRP (≥7 mg/L) at hospital discharge had significantly higher risk of disability and death at 3 months than those with CRP levels less than 7mg/L (Den Hertog et al, 2009). This pattern has also been demonstrated in IHD, with increased levels of CRP 10 weeks after a first episode of myocardial infarction being significantly predictive of future episodes of infarction or cardiovascular mortality (Marcinkowski et al, 2007).

It is possible that inflammation may act as a mediating variable in the afore-mentioned relationship between obesity and CVD. Evidence suggests a significant positive association between a variety of inflammatory markers and excess body weight (Pitsavos et al, 2007; Wee et al, 2008; Compher & Badellino, 2008; Agrawal et al, 2009). This relationship is strengthened by the fact that weight loss, achieved through diet or gastric surgery, is associated with significant reductions in CRP levels (Agrawal et al, 2009). Some evidence suggests that the adipose tissue itself, which has been recognized as an organ capable of regulating body processes and secreting hormones, may be responsible for the increased inflammation among obese individuals (Stenho-Bittel,

Table 6 - Summary of studies examining relationships between inflammation, obesity, physical activity and/or CVD

Authors and Year	Study Design	Study Population	Obesity, Physical Activity, Inflammation and CVD Measure	Results	Adjusted for
Cushman et al 2005	Prospective observ.	3971 M,F Age 65 years or older	BMI, WC CRP Low <1mg/L Intermediate 1-3 mg/L Elevated >3mg/L 2' analysis – CRP.10 MI, coronary death over 10 years Incidence	Low CRP: referent Intermediate: NS Elevated: **1.45** (1.14-1.86) PAR for elevated CRP was 11%	Age, sex, race, field center, HTN, diabetes, smoking, log pack-years, BMI, WC, total cholesterol, HDL, aspirin use
Marcinkowski et al 2007	Prospective observ.	107 M,F First acute MI Follow-up 18 months	BMI, waist circumference NA CRP, fibrinogen, sICAM-1, ESR, white blood cells, Chlamydia pneumoniae antibodies Blood levels drawn 10 days and 10 weeks post-MI Recurrence of MI, unstable angina pectoris, cardiac death	Higher CRP, ESR, sICAM-1 levels at 10 weeks associated with higher risk of MI recurrence Increased levels of these inflammatory markers at 10 weeks after initial acute MI are considered independent risk factors for future cardiovascular event recurrence	
Pitsavos et al 2007	Cross-sectional Part of ATTICA study	625 M 712 F Age 18-89 All have abdominal obesity	Frequency, duration and intensity of PA Expressed in Metabolic equivalents CRP	High CRP associated with lower PA, less likely to have a Mediterranean style diet Those with high CRP more likely to have high glucose, higher systolic and diastolic blood pressure, HTN, lower HDL, increased smoking habits, higher BMI, higher WC PA inversely correlated with CRP	Age, gender, BMI, glucose, lipids, BP

Table 6 - Summary of studies examining relationships between inflammation, obesity, physical activity and/or CVD (continued)

Authors and Year	Study Design	Study Population	Obesity, Physical Activity, Inflammation and CVD Measure	Results	Adjusted for
Panagiotakos et al 2008	ATTICA study Cohort	1514 M 1528 F Age 18-89 Greece	BMI, WC, HC, waist-to-hip ratio Self-reported weekly energy expenditure CRP, Amyloid A,	Increased age, waist-to-hip ratio, CRP, hypertension and diabetes were the most significant predictors of CVD development during follow-up	
Wee et al 2008	NHANES study Cohort	10492 M, F White, African-American and Hispanic Age >20	BMI, waist circumference CRP	In both sexes and all races, higher BMI and higher waist circumference significantly associated with higher CRP.	Age, education, health behaviours
Buckley et al 2009	Meta-analysis	23 studies included (prospective cohort, case-cohort, or nested case-control)	CRP (low defined as <1.0mg/L, average defined as 1.0-3.0mg/L, high defined as >3.0mg/L) Coronary death Nonfatal MI	RR 1.60 for high vs low CRP levels RR 1.26 for average vs low CRP levels	Studies adjusted for at least five of Age, sex, total cholesterol, HDL, smoking, systolic blood pressure, blood pressure medication
Arikawa et al 2010	Randomized Controlled Trial	319 F Age 18-30 Sedentary	BMI 16 week prescribed aerobic exercise program CRP, Adiponectin, leptin, Amyloid A	CRP levels in exercise group decreased by 1.41 mg/L CRP levels in control group decreased by 0.005 mg/L (p=0.04)	Change in body fat percent, change in fitness

BMI – Body mass index
CRP – C-reactive protein
ESR – erythrocyte sedimentation rate
HDL – high density lipoprotein
HTN – hypertension
LDL – low density lipoprotein
MI – myocardial infarction
sICAM-1 – soluble intercellular adhesion molecule
WBC – white blood cell
WC – waist circumference
WHR – waist to hip ratio

2008). Measures of abdominal obesity, like waist circumference and waist-to-hip ratio, show a particularly strong relationship with inflammation (Pitsavos et al, 2007; Wee et al, 2008).

It is also plausible that inflammation could play a mediating role in the relationship between physical activity and CVD. An analysis of the relationship between CRP and physical activity was completed with the data from the ATTICA study. Results showed a significant, inverse, dose-response relationship between physical activity and CRP (Pitsavos et al, 2007). In this population, individuals with high CRP were also more likely to have high blood glucose, hypertension, higher waist-to-hip ratio and higher levels of smoking (Pitsavos et al, 2007). Other evidence has also supported the relationship between physical activity and inflammation (Arikawa et al, 2010). It should be noted, however, that a recent intervention study in which subjects participated in a 6-month exercise program concluded that the significant improvements in CRP levels that were observed were actually associated with weight loss as opposed to increases in physical fitness (Stewart et al, 2010).

2.5 Summary

The variables that were examined in this literature review are the key variables involved in this study. In summary, the risk of CVD is associated with many factors, and the interactions between these variables can be complex; obesity has been shown to increase cardiovascular risk (Welborn et al, 2003; Yusuf et al, 2005; Li et al, 2006; Pardo Silva et al, 2006; Nusselder et al, 2009; Arnlov et al, 2010; Sehested et al, 2010), and physical activity has been shown to decrease risk (Mora et al, 2007; Nocon et al, 2008; Sofi et al, 2008; Kodoma et al, 2009). Although debate continues, it appears that even with high levels of physical activity, overweight and obese individuals will continue to experience greater cardiovascular risk than normal weight individuals. Therefore, the incorporation of physical activity into the life of an obese sedentary individual would have a protective effect on cardiovascular risk, but only a combination of physical activity and weight loss could fully eliminate the excess risk.

Additionally, the importance of inflammation, as both a predictive and prognostic tool, is increasingly being recognized. It is possible that inflammation may act as a mediating variable in the afore-mentioned relationships between obesity and CVD, and physical activity and CVD. In other words, inflammation may provide important insight into these complex and important relationships.

Ischemic heart disease is responsible for a large proportion of CVD morbidity and mortality. Therefore, although the majority of studies included in this literature review use the broader category of CVD morbidity or mortality as an outcome, the results from these studies also serve to inform the relationships between obesity, physical activity, inflammation and IHD.

Chapter 3

Objectives And Methods

3.1 Objectives and Hypotheses

3.1.1 Objectives

The three main objectives for this study are:

1. To determine:

    a) the association between excess body fat and excess abdominal fat, and incident IHD among men and women;

    b) the association between excess body fat and excess abdominal fat, and inflammatory markers among men and women;

    c) the association between inflammatory markers and incident IHD among men and women;

    d) how the relationship between excess body fat and excess abdominal fat, and incident IHD may be mediated by inflammatory markers among men and women.

2. To determine:

    a) the association between physical activity and incident IHD among men and women;

    b) the association between physical activity and inflammatory markers among men and women;

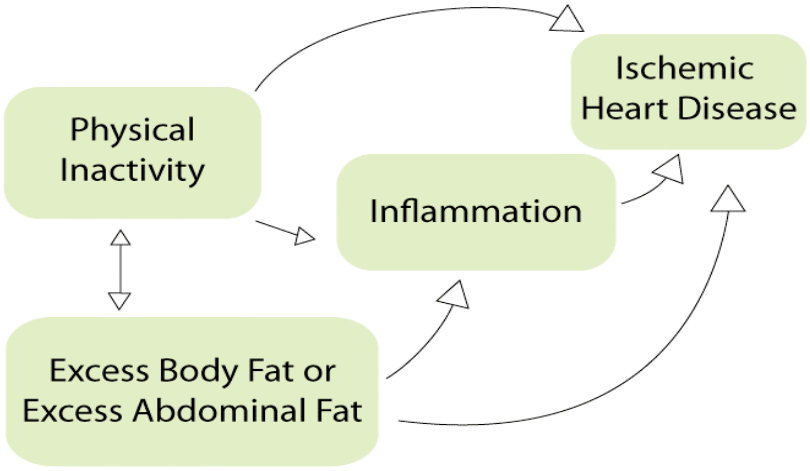
    c) how the relationship between physical activity and incident IHD may be mediated by inflammatory markers among men and women.

3. To create a final model describing the relationship between excess body fat and excess abdominal fat, physical activity, inflammatory markers and development of incident IHD.

3.1.2 Hypotheses

As seen in Figure 1, it is hypothesized that individuals with higher body fat (as measured by BMI) and greater abdominal obesity (as measured by waist circumference or waist-to-hip ratio) will be at increased risk of developing IHD compared to their lower-fat counterparts.

Figure 1 – Conceptual framework of the hypothesized relationship between excess body fat, physical activity, inflammatory markers and IHD



Similarly, it is predicted that individuals with lower levels of physical activity will be more likely to develop IHD than their active counterparts for any given body weight.

It is further hypothesized that inflammation will be a mediating variable in each of these relationships. These hypotheses are based on the related literature.

3.2 Methods

3.2.1 Overview

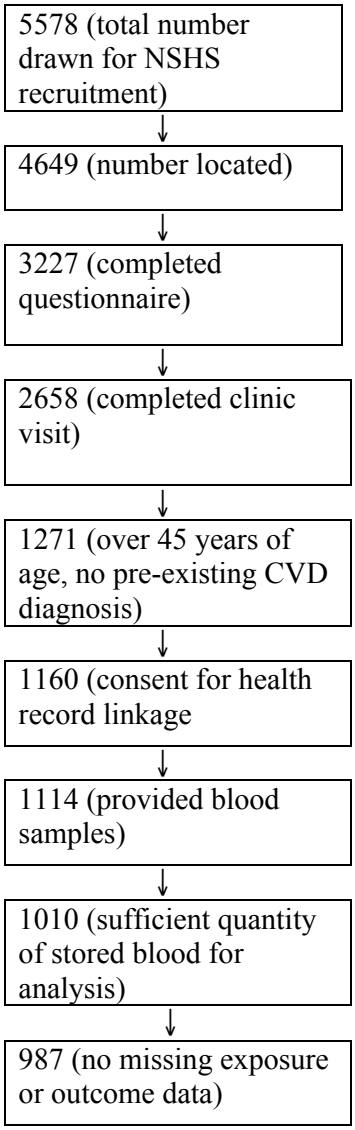
This project consists of a secondary analysis of data collected for a previous investigation that examined the relationship between depression, inflammatory markers and CVD (Davidson et al, 2009). Risk factors were measured during the 1995 Nova Scotia Health Survey (NSHS), which gathered health and lifestyle information on 2658 Nova Scotians. The outcomes, IHD morbidity and mortality, were measured by examining participants' hospitalization records and vital statistics between 1995 and 2005. The current project uses a subset of this linked data to examine the relationship between excess body fat, physical activity, inflammatory markers and development of IHD.

Certain inclusion criteria were applied for the previous study, which therefore apply to the present study. Because the risk of CVD events increases with age, and the presence of CVD events is very rare in individuals younger than 45 years of age, only individuals over 45 years of age were included. Additionally, the study was examining incident CVD, not recurrent disease, so individuals with pre-existing CVD were excluded. Of the 1271 participants over age 45 years without pre-existing CVD, one hundred eleven (9%) refused to provide consent for the linkage of their data with their health records. Blood samples were not available for 150 (12%) individuals, due to either their refusal or inappropriate handling of the samples. Twelve (0.9%) individuals were excluded because of incomplete depression scores, and 11 (0.8%) had no health outcome data available. These exclusions resulted in a sample size of 987.

Figure 2 describes the sample size reductions used in the previous study,

beginning with the initial 1995 NSHS recruitment.

Figure 2 - Reductions of sample size used in Davidson et al study



3.2.2 Data Sources

The afore-mentioned Davidson et al study, examining the relationship between inflammation, depression and CVD, linked baseline exposure data from the 1995 NSHS

with cardiovascular hospitalization data from the Canadian Institute for Health Information (CIHI) and mortality data from the Vital Statistics Database between 1995 and 2005. These databases were accessed via the Population Health Research Unit, housed in the Department of Community Health and Epidemiology at Dalhousie University. Blood samples that were drawn for the 1995 NSHS were analyzed by the Davidson et al study to obtain serum levels of the inflammatory markers CRP, ICAM and IL-6.

The 1995 NSHS was a population-based survey designed to assess the health of residents of Nova Scotia based on selected health indicators (physiological, psychosocial, demographic) and relevant health behaviors. This survey used a stratified-random sample with over-sampling of younger age groups and regions outside of Halifax (specifically, rural and remote areas). As described in Figure 2, 5578 Nova Scotians age 18 and over were selected using probability sampling methods from the provincial health insurance registry, the Medical Services Insurance database. Eighty-three percent of these individuals were located and contacted. Three percent of those located were not included due to pregnancy, breastfeeding, disability or significant ill-health. There were two components to the survey. The home interview was completed by 3227 subjects (72% of the remaining sample), and the clinic visit was completed by 2658 subjects (59%).

Data was collected by trained public health nurses during face-to-face interviews in the subjects' homes, as well as at clinic visits. The interview consisted of a trained nurse reading a structured questionnaire to the participant. On average, this took about 1.5 hours. During the clinic visit, height, weight and blood pressure were measured and a

blood sample was taken. All participants provided informed consent for participation, and signed an optional consent to link to health records. No information was gathered on individuals in the Royal Canadian Mounted Police, Canadian Military and First Nations natives on reserves because of their alternate sources of health insurance. Due to the relatively small representation of these groups in Nova Scotia, the sample who completed the original survey can be considered representative of the general provincial population (Nova Scotia Department of Health, 1996).

Development of CVD was measured by assessing the frequency of cardiovascular- or circulation-related hospitalizations, as identified by International Classification of Disease (ICD)-9 codes and ICD-10 codes. Mortality data were available through the vital statistics information which is collected regardless of whether the individual dies in a hospital, a long-term care facility or at home. International Classification of Disease-9 codes and ICD-10 codes were used to specify cause of death. Ischemic heart disease, as opposed to the broader category of CVD, was the focus of the current study because IHD makes up the majority of CVD. Other CVD outcomes, such as stroke and peripheral vascular disease, were not included because of the vast heterogeneity of CVD; there may be different mechanisms of action involved in these processes. Prior to beginning data analysis, the study proposal was evaluated by the Dalhousie University Health Sciences Research Ethics Board.

3.2.3. Measurement

3.2.3.1 Exposure Variables

Overweight and obesity was measured using BMI, waist circumference and waist-

to-hip ratio. These measurements were taken during the NSHS clinic visits. Physical activity was measured on the "Physical Activity" section on the 1995 NSHS. Questions assessed frequency of leisure time physical activity and incidental activity (flights of stairs climbed, city blocks walked) as well as participation in both light and strenuous sports. Regular physical activity was defined as exercising at least once per week. Participation in light and strenuous sports were each measured by hours of participation in the previous week. Following methods used by Davidson et al (2009), results from these individual physical activity-related questions were combined to estimate each individual's Paffenbarger physical activity score. This provides an estimation of weekly energy expenditure, and is measured in kilocalories per week.

Blood samples were collected and stored as part of the 1995 NSHS. As part of Dr. Davidson's National Institutes of Health-funded study on inflammation, depression and CVD risk, these samples were thawed and analyzed to obtain participants' baseline CRP, IL-6 and ICAM levels. Levels of CRP have been shown to remain stable during long-term storage, with a correlation of greater than 0.90 after 13 years (Ishikawa et al, 2007). A Dade Behring Cardiophase latex-enhanced immunonephelometry assay was used to measure the CRP levels, and a Quantikine high-sensitivity enzyme-linked immunosorbent assay kit was used to measure the levels of IL-6. Intercellular adhesion molecule levels were measured with a commercially-available enzyme-linked immunosorbent assay kit.

3.2.3.2 Outcome Variables

In this study, the morbidity and mortality outcomes are recorded as ICD-9 codes

(410.x – 414.x) and ICD-10 codes (I20.x – I25.x), corresponding to IHD. These ICD codes have adequate sensitivity and specificity to accurately represent the presence of their associated conditions (Birman-Deych, 2005).

3.2.3.3 Other Covariates

Data on additional covariates were collected during the 1995 NSHS, and were included in the statistical analysis to examine their potential influence on the relationships of interest. Diet, however, is a potentially important covariate for which we had little or no exposure data. Diet is often an important contributor to obesity, and certain aspects of diet have been associated with risk of CVD development. Although the 1995 NSHS collected minimal information on diet, it did assess serum cholesterol and triglyceride levels, which capture a component of diet.

Hypertension is a risk factor for cardiovascular disease and may be influenced by both physical activity and obesity. Blood pressure was measured by study nurses twice during the 1995 NSHS clinic visit, and the two readings were averaged. Information on presence of diabetes was also gathered, as diabetes may be associated with both the exposures and outcome of interest.

Alcohol intake and smoking were examined to determine their importance as covariates. Smoking behaviour was assessed with the survey question, "At the present time, do you smoke cigarettes?" Alcohol consumption, as measured by number of drinks per week, was not included in the final analysis because of the very high rate of missing observations (34.1%).

Because family history can contribute to CVD or obesity development, and likely

influences physical activity habits, data on parental history of heart attack prior to age 60 years was included in the analysis.

3.2.4 Statistical Analysis

All statistical analyses were conducted using SPSS, version 17.0, available through the Department of Community Health and Epidemiology at Dalhousie University. Descriptive statistics were performed initially. The variables were examined to determine their ranges and assess the data for outliers. Each of the continuous variables was examined graphically using probability plots to determine whether it was normally distributed.

The sample was divided into physically active and physically inactive groups. A Paffenbarger score of 1000 kcal/week was used as the cut-off point, based on evidence in the literature (Warburton et al, 2008). The characteristics of the two groups, physically active and physically inactive, were compared to determine similarities and differences between the two groups. The sample was then divided into overweight and non-overweight groups, using the standard BMI cut-off of 25 kg/m^2 (Health Canada, 2003), and the two groups were compared. Differences between continuous, normally distributed variables were analyzed using Student T-tests, while those that were not normally distributed were analyzed using the Mann-Whitney Test. Differences between categorical variables were assessed using Chi-square tests. Statistical significance was assessed based on a p-value of less than 0.05.

Analytic statistics were used to determine the role of inflammation in the relationship between obesity and IHD, and physical activity and IHD. Cox proportional

hazards regression, a form of survival analysis, was used because although most of the participants entered the study at the same time, those experiencing incident IHD events exited the study at different times. Therefore, this method of analysis accounted for the differences in length of follow-up between the participants.

Two of the options available in the SPSS software were used when building the statistical models. The Enter method forced all selected variables into the final model. It ensured that a relative risk and p-value would be displayed for each variable, regardless of whether or not it was statistically significantly associated with the outcome. The Forward Stepwise Likelihood Ratio was used when only the statistically significant results were of interest. With this option, a variable entered the regression model if its inclusion caused a significant ($p<0.05$) change in the -2 Log Likelihood from the previous step or block. The variable remained in the model if its removal caused a significant ($p<0.10$) change in the -2 Log Likelihood. All analytic statistics were completed separately for males and females.

Because the units of the fat-related variables differ, standardization of the variables was performed to allow for a more appropriate comparison of each variable's individual association with IHD. When a variable is standardized using a Z-score, its mean becomes zero and each standard deviation becomes 1.0.

To provide information about the relative importance of obesity, physical activity and inflammation in IHD risk at the population level, the Population Attributable Risk % was calculated. For each key risk factor, this was done by subtracting the proportion of unexposed individuals who developed IHD from the total proportion of individuals who developed IHD, and then dividing by the total proportion of individuals who developed

IHD. This number was then multiplied by 100 to obtain the Population Attributable Risk % (Oleckno, 2002).

Chapter 4

Results

4.1 Descriptive Statistics

There were 8181 person-years of follow-up data available for analysis. The average length of follow-up was 8.27 years. One hundred forty-eight incident IHD events occurred: 81 among the 474 males (5 of which were fatal) and 67 among the 515 females (5 of which were fatal).

The group of 989 males and females was explored to examine some of the characteristics of the sample. It was determined that BMI, Paffenbarger physical activity score, triglycerides, ICAM, IL-6 and CRP were not normally distributed, and therefore the median, interquartile range (IQR) and Mann-Whitney test were used in the descriptive analyses of these variables. Baseline characteristics of the sample are displayed in Table 7. When missing data resulted in calculations being completed with fewer than 989 subjects, the number is specified.

The mean age of the participants was 62 years. The mean BMI of participants was 27, which is classified by Health Canada (2003) as overweight. Twenty percent of the sample reported that they were current smokers, and the average number of drinks in the last week was 3.5. Over one quarter of the participants reported that their occupational level was in executive, administrative, managerial or professional.

As mentioned, the sample used in the 1995 Nova Scotia Health Survey was considered representative of the overall Nova Scotia population. To determine whether the subset of 987 used in this study remained similar to the original survey sample, the groups were compared on key demographic characteristics (see Table 8).

Table 7 - Baseline characteristics of population-based sample of 989 ischemic heart disease-free men and women, age 45 to 98 years (1995 NSHS)

Variable		Mean (SD), Median (IQR) or % (Number), specified by superscripts
Age (years) [1]		61.7 (11.6)
Length of follow-up (years) [1]		8.3 (2.8)
Sex	Males	48 (474)
	Females	52 (515)
BMI (kg/m^2) [2]		27.0 (6.5)
Waist circumference (cm) [1] n=986	Males	98 (11.9)
	Females	86 (13.2)
Waist-to-hip ratio [1] n=986	Males	1.0 (0.1)
	Females	0.8 (0.1)
Paffenbarger score (kcal/week) [2]		1400 (2700)
Inflammatory markers	CRP (mg/L) [2] n=986	2.2 (3.7)
	ICAM (ng/mL) [2] n=987	340 (190)
	IL-6 (pg/mL) [2] n=978	1.4 (1.5)
Cholesterol	Total cholesterol (mmol/L) [1]	5.7 (1.1)
	LDL (mmol/L) [1] n=953	3.5 (0.9)
	HDL (mmol/L) [1]	1.3 (0.4)
	Triglycerides (mmol/L) [2]	1.7 (1.2)
Blood pressure [1]	Systolic (mmHg) n=988	132 (17)
	Diastolic (mmHg) n=986	79 (9)
Number of drinks in last week [1] n = 652		3.5 (6.3)
Current smoker [3]		20 (202)
Diabetes Mellitus [3]		6.1 (60)
Medication Use [3]	Aspirin	6.2 (61)
	Lipid-lowering	2.4 (24)
	Anti-hypertensive	19 (189)
Occupational level [3] n=887	Executive, administrative, managerial, professional	28 (274)
	Technical and related support	5.3 (52)
	Administrative support	9.9 (98)
	Marketing, sales, service	23 (231)
	Agricultural, forestry, fishing, craft, repair, labour	24 (232)

[1] Mean (SD) reported
[2] Median (IQR) reported
[3] Percent (Number) reported

Table 8 - Comparison of original sample from 1995 Nova Scotia Health Survey with sample from current study on key demographic characteristics

Variable	Means or proportions in current study n=989	Means or proportions among males and females ≥35 years, in 1995 Nova Scotia Health Survey* n=1836
Males (%)	48	49
Overweight (%) (BMI >25 kg/m2)	66	63
Inactive (%) (report no physical activity, or Paffenbarger score <1000 kcal/week)	42	45
Total cholesterol (mmol/L)	5.7	5.5
HDL cholesterol (mmol/L)	1.3	1.3
LDL cholesterol (mmol/L)	3.5	3.4
Triglycerides (mmol/L)	2.0	1.9
High blood pressure (%) (>140/90 mmHg and/or on anti-HTN medication)	23	38
Regular smoking (%)	20	24
Diabetes (%)	6	7

Data from the 1995 Nova Scotia Health Survey Executive Summary (Nova Scotia Department of Health & Heart Health Nova Scotia, 1996)

The sample for the current study was limited to individuals >45 years of age with no prior history of IHD, while the calculations for the Nova Scotia Health Survey sample was performed on individuals ≥35 years, due to the age group divisions presented. In the current sample compared to the original sample, there appeared to be roughly similar proportions of overweight and obese individuals (66% and 63%), regular smokers (20% and 24%), and diabetes (6% and 7%). High blood pressure, as defined by a blood pressure greater than 140/90 mmHg and/or use of anti-hypertension medication, was more prevalent in the original sample versus the current study sample (38% compared to

23%). There appeared to be a similar proportion of inactive individuals (42% compared to 39%), however in the 1995 Nova Scotia Health Survey this was defined as reporting no participation in physical activity and in the current study this was defined as a Paffenbarger Score of less than 1000 kcal/week. On the majority of these characteristics, the current study sample appeared to be very similar to the original sample and therefore it is likely that the current study remains representative of the broader Nova Scotia population.

The study group was then divided into normal weight and overweight subjects according to BMI, and T-tests, Chi Square statistics and Mann-Whitney tests were used to determine if the groups differed with respect to any of the variables of interest. Results are displayed in Table 9.

The overweight subjects in this sample differed significantly from the normal weight subjects with respect to age, sex, CRP, IL-6, HDL, triglycerides, systolic blood pressure, diastolic blood pressure and reported alcohol consumption. Overall, the overweight individuals compared to the normal weight individuals were 3.3 years younger, had serum HDL measurements 0.2 mmol/L lower, serum triglycerides measurements 0.5 mmol/L higher, systolic blood pressure readings 6 mmHg higher, diastolic blood pressure readings 6 mmHg higher and reported consuming approximately 1.0 more alcoholic drinks per week. These findings suggest that the overweight subjects appear to have increased cardiovascular risk compared to the normal weight subjects. Fifty-one percent of the overweight group was male and 49% was female, while the normal weight group was made up of 41% males and 59% females. There were no significant differences noted between the overweight and normal weight groups' physical

activity scores, LDL or total cholesterol measurements, years of schooling, reported smoking behavior, diabetes prevalence or occupation level.

The group was then divided by physical activity according to a cut-off value of 1000 kcal/week, which is an established cut-off point for the definition of moderate participation in physical activity (see Section 2.2 of the Literature Review). Results are displayed in Table 10. The inactive subjects, on average, fared worse than active subjects; they were 4.4 years older, had triglyceride readings 0.6 mmHg higher, BMI values 1.0 kg/m^2 higher, systolic blood pressure measurements 5 mmHg higher, and 0.4 fewer years of schooling compared to the active subjects. Forty percent of the inactive group was male and 60% was female, while the active group contained 53% males and 47% females. The groups did not differ significantly with respect to serum cholesterol, LDL or HDL results, diastolic blood pressure, reported alcohol consumption, reported smoking behavior, diabetes prevalence or occupational level.

Table 9 – Comparison of variables between normal weight and overweight groups according to BMI (1995 NSHS)

Variable		Mean (SD), Median (IQR) or Percent (Number), specified by superscripts		Significance
		Normal weight (BMI =<24.9 kg/m^2) n=333	**Overweight (BMI =>25.0 kg/m^2) n=656**	
Age (years) [1]		63.9 (11.9)	60.6 (11.2)	0.000
Male [3]		41 (137)	51 (337)	0.002
Paffenbarger score (kcal/week) [2]		1500 (2500)	1300 (2800)	0.667
CRP (mg/L) [2] n=986		1.4 (2.7)	2.6 (4.5)	0.000
ICAM (ng/mL) [2] n=987		339 (192)	343 (188)	0.273
IL-6 (pg/mL) [2] n=978		1.2 (1.5)	1.5 (1.5)	0.000
Total cholesterol (mmol/L) [1]		5.6 (1.0)	5.8 (1.1)	0.058
LDL (mmol/L) [1] n=953		3.5 (0.9)	3.6 (0.9)	0.455
HDL (mmol/L) [1]		1.4 (0.4)	1.2 (0.3)	0.000
Triglycerides (mmol/L) [2]		1.4 (0.9)	1.9 (1.3)	0.000
Systolic blood pressure (mmHg) [1] n=988		128 (17)	134 (17)	0.000
Diastolic blood pressure (mmHg) [1] n=986		75 (8)	81 (9)	0.000
Number of drinks in last week [1] n=652		2.8 (5.3)	3.8 (6.7)	0.041
Current smoker [3]		23 (77)	19 (125)	0.134
Diabetes [3]		5.7 (19)	6.3 (41)	0.735
Aspirin medication [3]		7.2 (24)	5.6 (37)	0.333
Lipid-lowering medication [3]		1.5 (5)	2.9 (19)	0.178
Anti-hypertensive medication [3]		16 (54)	21 (135)	0.099
Education (years) [3] n=982		3.7 (12)	2.5 (12)	0.980
Occupation level [3] n=887	Executive, managerial and professional	29 (95)	27 (179)	0.092
	Technicians	4.8 (16)	5.5 (36)	
	Administrative support	12 (39)	9.0 (59)	
	Marketing, sales and service	26 (85)	22 (146)	
	Agriculture, forestry, craft, repair, labour	19 (62)	26 (170)	

[1] Mean (SD) reported
[2] Median (IQR) reported
[3] Percent (Number) reported

Table 10 – Comparison of variables between active and inactive groups according toPaffenbarger physical activity score (1995 NSHS)

Variable		Mean (SD), Median (IQR) or Percent (Number), specified by superscripts		Significance
		Active (Paffenbarger Score >=1000 kcal/week) n = 578	Inactive (Paffenbarger Score <1000 kcal/week) n = 411	
Age (years) [1]		59.9 (10.6)	64.3 (12.4)	0.000
Male [3]		53 (308)	40 (166)	0.000
BMI (kg/m2) [2]		26.7 (5.8)	27.7 (7.7)	0.004
Waist circumference (cm) [1] n=978		90 (13)	93 (15)	0.001
Waist-to-hip ratio [1] n=978		0.9 (1.0)	0.9 (1.0)	0.174
CRP (mg/L) [2] n=986		1.7 (2.8)	3.2 (4.8)	0.000
ICAM (ng/mL)[2] n=987		331 (163)	361 (216)	0.003
IL-6 (pg/mL) [2] n=978		1.2 (1.2)	1.8 (2.0)	0.000
Total cholesterol (mmol/L) [1]		5.6 (1.0)	5.8 (1.1)	0.060
LDL (mmol/L) [1] n=953		3.5 (0.9)	3.6 (1.0)	0.319
HDL (mmol/L) [1]		1.3 (0.4)	1.3 (0.4)	0.405
Triglycerides (mmol/L) [2]		1.2 (1.1)	1.8 (1.3)	0.000
Systolic blood pressure (mmHg) [1] n=988		130 (17)	135 (18)	0.000
Diastolic blood pressure (mmHg) [1] n=986		79 (9)	79 (10)	0.837
Number of drinks in last week [1] n=652		3.8 (6.2)	3.1 (6.4)	0.163
Current smoker [3]		19 (107)	23 (95)	0.077
Diabetes [3]		5.0 (29)	7.5 (31)	0.101
Aspirin use [3]		5.5 (32)	7.1 (29)	0.328
Lipid-lowering med use [3]		2.2 (13)	2.7 (11)	0.667
Anti-hypertensive med use [3]		16 (91)	24 (98)	0.001
Education (years) [3] n=982		3.7 (12.1)	3.3 (11.4)	0.001
Occupation level [3] n=887	Executive, managerial and professional	29 (169)	26 (105)	0.308
	Technicians	6.2 (36)	3.9 (16)	
	Administrative support	11 (61)	9.0 (37)	
	Marketing, sales and service	22 (127)	25 (104)	
	Agriculture, forestry, craft, repair, labour	24 (139)	23 (93)	

[1] Mean (SD) reported

[2] Median (IQR) reported

[3] Percent (Number) reported

4.2 Analytic Statistics

4.2.1 Overview

For clarity, the results of the analytic statistics will be presented under the headings of the study objectives. As previously described, these objectives are:

1. To determine:
    a) the association between excess body fat and excess abdominal fat, and incident IHD among men and women;
    b) the association between excess body fat and excess abdominal fat, and inflammatory markers among men and women;
    c) the association between inflammatory markers and incident IHD among men and women;
    d) how the relationship between excess body fat and excess abdominal fat, and incident IHD may be mediated by inflammatory markers among men and women.
2. To determine:
    a) the association between physical activity and incident IHD among men and women;
    b) the association between physical activity and inflammatory markers among men and women;
    c) how the relationship between physical activity and incident IHD may be mediated by inflammatory markers among men and women.
3. To create a final model describing the relationship between excess body fat and excess abdominal fat, physical activity, inflammatory markers and development of incident IHD.

As described in the methods section, Cox Proportional Hazards Regression was used when calculating the results for the objectives. This statistical method provides relative risks for each variable that are interpreted as the change in outcome risk for each one-unit change in the independent variable. As presented in Table 11, however, a variable like the Paffenbarger physical activity score has a range measured in ten thousands, while a variable like the waist-to-hip ratio has a range measured in tenths or hundredths. Multiplying or dividing these variables by factors of 10 can provide results that are more easily interpretable, without affecting their underlying associations with the outcome variable. For example, it is more practical to express the change in IHD risk for a 1000 kcal/week increase in activity than for a 1kcal/week increase in activity. This is an established practice when dealing with variables of this nature (Panagiotakos et al, 2008; Tseng et al, 2008).

Therefore, based on the ranges displayed in Table 11, three variables were modified in this way. The ICAM was divided by 10, which changed its range from 1939.87 to 193.99. The waist-to-hip ratio was multiplied by 10, which changed its range from 0.74 to 74.39. Finally, the Paffenbarger physical activity score was divided by 1000, changing its range from 27080 to 270.80.

Table 11 also displays the normal values for each of the variables listed. These normal values do not represent the mean of the general population; instead, these are values reflecting a normal level of cardiovascular risk. For this reason it is possible for the sample mean to fall outside of the normal value for a given variable.

To account for the fact that elevated CRP levels often occur in the presence of acute infection, the individuals with CRP levels greater than or equal to 10 mg/L were

excluded for the following analyses. Among males, this resulted in 39 subjects being excluded, leaving 435 for the analysis. Among the females, 51 individuals were excluded due to CRP levels greater than or equal to 10mg/L, leaving 464 for the final analysis.

The correlations between the body fat- and abdominal fat-related variables, physical activity and inflammatory markers were then examined using Pearson Correlation Coefficients (Table 12). Results showed that for both males and females, the waist circumference and hip circumference were each highly correlated with each other and with BMI (correlation coefficients >0.7; p=0.000). Because of concerns with including highly correlated variables in multivariate regression models, it was determined that of the four body fat- and abdominal fat-related variables, BMI and waist-to-hip ratio would be used in the analysis. These two variables were not as highly correlated with each other (0.47 for males, 0.25 for females), and according to the literature review they are the most commonly used and the most likely to be significantly associated with the IHD outcome.

Table 11 – Exploration of range, minimum, maximum and mean or median values for independent variables and potential confounding variables among males and females (1995 NSHS)

Variable	Mean (SD) or Median (IQR)	Range (Min – Max)	Values indicating normal cardiovascular risk
Age (years) [1]	62 (12	53 (45 – 98)	
BMI (kg/m2) [2]	27 (6.5)	65 (13 – 78)	18.5 - 24.9 (Health Canada, 2003)
Waist circumference (cm) [1]	86 (13)	84 (59 –143)	M <102 F <88 (Health Canada, 2003)
Waist-to-hip ratio [1]	0.8 (0.08)	0.7 (0.6 – 1.3)	M <1.0 F <0.85 (World Health Organization, 2000)
Paffenbarger score (kcal/week) [2]	1400 (2700)	27000 (0.0 – 27000)	>1000 (Warburton et al, 2008)
CRP (mg/L) [2]	2.2 (3.7)	98 (0.08 – 98)	<3.0 (Pearson et al, 2003)
ICAM (ng/mL) [2]	341 (188)	1940 (2.7 –1940)	<270 (Ponthieux et al, 2003)
IL-6 (pg/mL) [2]	1.4 (1.5)	290 (0.08 – 290)	<1.78 (Volpato et al, 2001)
Total cholesterol [1] (mmol/L)	5.7 (1.1)	8.0 (2.2 – 10)	<5.2 (Heart & Stroke Foundation, 2003)
LDL (mmol/L) [1]	3.5 (0.9)	6.2 (0.5 – 6.7)	<3.5 (Heart & Stroke Foundation, 2010)
HDL (mmol/L) [1]	1.3 (0.4)	3.1 (0.5 – 3.6)	M >1.0 F >1.3 (Heart & Stroke Foundation, 2010)
Triglycerides (mmol/L) [2]	1.7 (1.2)	15.0 (0.4 – 15.4)	<1.7 (Heart & Stroke Foundation, 2010)
Systolic blood pressure (mmHg) [1]	132 (17)	105 (94– 199)	<140 (Heart & Stroke Foundation, 2003)
Diastolic blood pressure (mmHg) [1]	79 (9)	59 (54 – 113)	<90 (Heart & Stroke Foundation, 2003)

[1] Mean (SD) reported
[2] Median (IQR) reported

Table 12 – Pearson Correlation matrix of body fat- and abdominal fat-related variables, physical activity variable and inflammatory markers

Variables		BMI (kg/m2)	Waist circ. (cm)	Hip circ. (cm)	Waist-to-hip ratio	Paffenbarger Score	IL-6 (pg/mL)	ICAM (ng/mL)
Waist circ. (cm)	Males	0.83 (0.00)*	.					
	Females	0.80 (0.00)*	.					
Hip circ. (cm)	Males	0.77 (0.00)*	0.83 (0.00)*	.				
	Females	0.86 (0.00)*	0.76 (0.00)*	.				
Waist-to-hip ratio	Males	0.50 (0.00)*	0.73 (0.00)*	0.23 (0.00)*	.			
	Females	0.24 (0.00)*	0.65 (0.00)*	0.01 (0.88)	.			
Paffenbarger Score (kcal/week)	Males	-0.06 (0.19)	-0.13 (0.00)*	-0.09 (0.06)*	-0.12 (0.01)*	.		
	Females	-0.09 (0.04)*	-0.09 (0.05)*	-0.03 (0.58)	-0.16 (0.00)*	.		
IL-6 (pg/mL)	Males	0.02 (0.73)	0.04 (0.43)	0.01 (0.80)	0.05 (0.28)	0.07 (0.14)	.	
	Females	0.01 (0.83)	0.02 (0.62)	0.01 (0.84)	-0.02 (0.72)	0.03 (0.54)	.	
ICAM (ng/mL)	Males	0.04 (0.37)	0.10 (0.05)*	0.08 (0.11)	0.07 (0.16)	-0.04 (0.40)	0.05 (0.32)	.
	Females	0.10 (0.04)*	0.11 (0.02)*	0.12 (0.01)*	0.09 (0.07)	-0.00 (0.97)	0.03 (0.50)	.
CRP (mg/L)	Males	0.25 (0.00)*	0.33 (0.00)*	0.20 (0.00)*	0.32 (0.00)*	-0.18 (0.00)*	0.11 (0.02)*	0.16 (0.00)*
	Females	0.24 (0.00)*	0.39 (0.00)*	0.20 (0.00)*	0.18 (0.00)*	-0.13 (0.01)*	0.00 (0.95)	0.07 (0.15)

*Statistically significant at an alpha value of 0.05

4.2.2 Results for Objectives

1.a) Relationship between excess body fat and/or excess abdominal fat and IHD

The relationship between excess body fat and/or excess abdominal fat and IHD was explored using hazards regression. The waist circumference, hip circumference, waist-to-hip ratio and BMI variables were each entered into a Cox Proportional Hazards regression model with IHD for men and women separately.

Neither of the fat-related variables was significant for males. The waist-to-hip ratio variable was the only fat-related variable that was significantly related to the IHD outcome in females. As seen in Table 13, the relative risk for the waist-to-hip ratio variable for females was 1.50 [1.19 – 1.89], indicating that an increase in the waist-to-hip ratio of 0.10 would be associated with a 50% increase in incident IHD risk. None of the other excess body fat and/or excess abdominal fat variables had associations with the IHD outcome that were statistically significant at an alpha level of 0.05.

Table 13 – Crude association between measures of body fat and/or abdominal fat and IHD for males and females using univariate Cox Proportional Hazards Regression models

Variable	RR [95% CI]	
	Males	**Females**
BMI (kg/m2)	1.03 [0.99 – 1.08]	1.01 [0.96 – 1.06]
Waist-to-hip ratio (0.1 unit)	1.41 [0.99 – 2.00]	1.50 [1.19 – 1.89]

Because each variable was measured in different units, it was important to examine each of the variables using standardized Z-scores to allow for greater

comparability. As displayed in Table 14, when the relative risks of the standardized fat-related variables were compared, the waist-to-hip ratio variable remained the most significantly associated with IHD for the females. For the males, although neither of the fat-related variables had statistically significant results, the magnitude of the effect estimate was larger for the waist-to-hip ratio than for the BMI.

Table 14 - Associations between standardized obesity indicators and incident IHD among males and females using both univariate and multivariate Cox Proportional Hazards Regression models

Standardized variable	**Univariate model RR [95% CI]**		**Multivariate model RR [95% CI]**	
	Males	**Females**	**Males**	**Females**
BMI (kg/m2)	1.18 [0.94 – 1.49]	1.03 [0.78 – 1.36]	1.12 [0.83 – 1.48]	0.96 [0.73 – 1.27]
Waist-to-hip ratio (0.1 unit)	1.24 [0.99 – 1.56]	1.40 [1.15 – 1.69]	1.19 [0.92 – 1.54]	1.40 [1.16– 1.69]

1.b) Relationship between excess body fat and/or excess abdominal fat and inflammatory markers

Pearson correlation coefficients were calculated to examine the associations between each of the body fat and/or abdominal fat-related variables and each of the inflammatory marker variables. Results, seen in the correlation matrix in Table 12, show that waist circumference, hip circumference, waist-to-hip ratio and BMI are each significantly associated with CRP for both males and females. For males, ICAM was significantly associated with waist circumference, while for females, ICAM was significantly associated with waist circumference, hip circumference and BMI. Although the strengths of the correlations are not high, they are all in a positive direction,

suggesting that increased values of the fat-related variables are associated with increased values of the inflammatory markers Among the males and females in this sample, none of the body fat and/or abdominal fat-related indicators was significantly associated with IL-6.

1.c) Relationship between inflammation and IHD

Initially, to examine the relationship between inflammatory markers and IHD, each inflammatory marker was tested with the IHD outcome in a univariate hazards regression model. As seen in Table 15, none of the inflammatory markers was statistically significantly associated with the outcome for the males, and among the females both ICAM and CRP showed statistically significant results, with relative risks of 1.02 [95% CI 1.01 – 1.03] and 1.13 [1.02 – 1.24], respectively.

Table 15 – Crude associations between inflammatory markers and incident IHD outcomes among males and females using univariate Cox Proportional Hazards Regression models

Variable	**Crude Association RR [95% CI]**	
	Males	**Females**
CRP (mg/L)	1.06 [0.96 – 1.16]	1.13 [1.02 – 1.24]
IL-6 (pg/mL)	1.00 [0.97 – 1.03]	1.00 [0.96 – 1.03]
ICAM (10 ng/mL)	1.01 [0.99 – 1.02]	1.02 [1.01 – 1.03]

Each inflammatory marker was again standardized to Z-scores and was tested independently with IHD using univariate hazards regression (Table 16). Although none of the results for males were statistically significant at an alpha level of 0.05, the CRP

appeared to be the inflammatory marker with the strongest association with the IHD outcome.

Table 16 – Associations between standardized inflammatory markers and incident IHD among males and females using both univariate and multivariate Cox Proportional Hazards Regression models

Standardized Variable	Univariate model RR [95% CI]		Multivariate model RR [95% CI]	
	Males	**Females**	**Males**	**Females**
CRP (mg/L)	1.46 [0.76 – 2.82]	2.19 [1.16 – 4.14]	1.47 [0.74 – 2.90]	2.10 [1.09 – 4.05]
IL-6 (pg/mL)	0.99 [0.74 – 1.32]	0.93 [0.55 – 1.57]	0.96 [0.68 – 1.37]	0.88 [0.37 – 2.10]
ICAM (10 ng/mL)	1.12 [0.90 – 1.40]	1.44 [1.16 – 1.79]	1.12 [0.88 – 1.38]	1.42 [1.14 – 1.77]

Among females, after standardization both ICAM and CRP remained significantly associated with IHD in the univariate models, with relative risks of 1.44 [1.16 – 1.79] and 2.19 [1.16 – 4.14], respectively. When all the standardized variables were combined in a multivariate hazards regression model with IHD, the relative risks for each of the variables were slightly decreased. Intercellular Adhesion Molecule, with a relative risk of 1.42 [1.14 – 1.77], and CRP, with a relative risk of 2.10 [1.09 – 4.05], both remained significant. Examination of the magnitudes of these relative risks suggest that CRP is the inflammatory marker most significantly associated with IHD for the females.

1. d) How the relationship between excess body fat and excess abdominal fat and IHD may be mediated by inflammatory markers

To determine the relationship between excess body fat and/or excess abdominal fat, inflammatory markers and IHD, a Cox Proportional Hazards Regression model was created. The first block of the model contained the waist-to-hip ratio, which, according to the previous analyses, was the abdominal fat-related variable most strongly associated with IHD for both males and females. The second block contained CRP, which had also been determined in previous analyses to be the inflammatory markers most strongly associated with IHD for both males and females. Results are displayed in Table 17. Among males, neither of these variables reached statistical significance and therefore were not incorporated into the final model.

Table 17 – Multivariate Cox Proportional Hazards Regression model including body fat- and/or abdominal fat-related variables, inflammatory markers and IHD development for males and females

Variable	**RR [95% CI]**	
	Males	**Females**
Waist-to-hip ratio (0.1 unit)	1.36 [0.93 – 1.98]	1.48 [1.15 – 1.90]
CRP (mg/L)	1.03 [0.93 – 1.14]	1.11 [1.00 – 1.22]

Results for females are also displayed in Table 17. Waist-to-hip ratio, with a relative risk of 1.48 [1.15 – 1.90] was found to be significantly associated with development of IHD. This relative risk is slightly decreased from the 1.50 [1.19 – 1.89] that was found when waist-to-hip ratio was the only variable in the hazards regression model. The multivariate association between CRP and IHD (1.11 [1.00 – 1.22]) was also slightly decreased from its univariate association with IHD (1.13 [1.02 – 1.24]).

2.a) The relationship between physical activity and IHD

In the next series of analyses, the relationship between physical activity and IHD was explored using hazards regression. The sole measure of physical activity was the Paffenbarger Score. The borderline statistically significant relative risk of 0.92 [0.85 – 1.00], seen in Table 18, suggests that increased amounts of physical activity were associated with decreased risks of IHD in this sample of males. A similar, although not statistically significant, protective association was seen for females.

Table 18– Association between physical activity as measured by Paffenbarger score and IHD development for males and females using univariate Cox Proportional Hazards Regression models

Variable	**RR [95% CI]**	
	Males	**Females**
Paffenbarger score (1000 kcal/week)	0.92 [0.85 – 1.00]	0.90 [0.78 – 1.03]

2.b) The relationship between physical activity and inflammatory markers

Pearson correlation coefficients were used to determine the association between physical activity and each of the inflammatory markers. As seen in the correlation matrix in Table 12, CRP was the only inflammatory marker that showed a statistically significant association with physical activity for both males and females. The negative values of the correlation coefficients indicate that increased amounts of physical activity are associated with decreased levels of serum CRP.

2.c) How the relationship between physical activity and IHD may be mediated by inflammatory markers

To explore the relationship between physical activity, inflammatory markers and IHD, Cox Proportional Hazards Regression was used. The first block contained physical activity, and the second block contained CRP. As displayed in Table 19, the only variable that retained borderline statistical significance in the final model for males was physical activity. It was in the protective direction. The results for CRP were not statistically significant and therefore were not incorporated into the model.

Table 19 – Cox Proportional Hazards Regression model including physical activity, inflammatory markers and IHD development among males and females

Variable	**RR [95% CI]**	
	Males	**Females**
Paffenbarger score (1000 kcal/week)	0.92 [0.85 – 1.00]	0.91 [0.80 – 1.04]
CRP (mg/L)	1.04 [0.94 – 1.14]	1.13 [1.02 – 1.24]

Also seen in Table 19, the results for females show that physical activity was not statistically significant in the final model, while CRP did remain statistically significant. .

3. Final model describing the relationship between excess body fat and excess abdominal fat, physical activity, inflammatory markers and development of incident IHD

The final series of analyses explored the multivariate associations between excess

body fat and/or excess abdominal fat, physical activity and inflammation with respect to IHD risk in a Cox Proportional Hazards Regression model. Waist-to-hip ratio was shown in previous analyses to be the body fat-related variable most significantly associated with IHD for both males and females, and similarly, CRP was the inflammatory marker most significantly associated with IHD for males and females.

Table 20 – Cox Proportional Hazards Regression model incorporating waist-to-hip ratio, physical activity and inflammatory markers among males and females

Category	Variable	RR [95% CI]	
		Males	**Females**
Obesity indicator	Waist-to-hip ratio (0.1 unit)	1.31 [0.90 – 1.91]	1.45 [1.12 – 1.86]
Physical Activity	Paffenbarger score (1000 kcal/week)	0.93 [0.86 – 1.00]	0.93 [0.82 – 1.06]
Inflammatory marker	CRP (mg/L)	1.02 [0.92 – 1.12]	1.10 [1.00 – 1.21]

Among the males, only the Paffenbarger score was borderline statistically significantly associated with IHD in this multivariate model (Table 20). Among females, the Paffenbarger score was not statistically significant, but both the waist-to-hip ratio and CRP significantly contributed to the model. The relative risk of 1.45 [1.12 – 1.86] for the waist-to-hip ratio indicates that an increase of 0.10 in the waist-to-hip ratio would be associated with an increased IHD risk of approximately 45%. Similarly, the relative risk of 1.10 [1.00 – 1.21] for CRP suggests that an increase of 1.0 mg/L would be associated with an increased IHD risk of approximately 10%. Although the physical activity variable did not have a statistically significant association with IHD in this model, the effect estimate was in the protective direction.

4.2.3 Supplementary Analysis – Independent IHD Risk Factors

Although there are additional covariates that have well-established associations with IHD development, the objectives for this study focused on the specific risk factors of obesity, physical activity and inflammatory markers. Additional covariates, including blood pressure, cholesterol, age, family history, medication use, smoking, diabetes and alcohol, are traditionally included in regression models for IHD. Therefore, although it did not provide additional information regarding the objectives of this study, a supplementary multivariate regression model that included additional covariates was created.

This supplementary model was created in an identical manner to the model displayed in Table 20, with the addition of a fourth block containing the following covariates: mother's history of heart disease prior to age 60, father's history of heart disease prior to age 60, cholesterol, LDL, HDL, triglycerides, diastolic blood pressure, systolic blood pressure, age, years of education, use of aspirin, use of lipid-lowering medication, use of anti-HTN medication, regular cigarette smoking and diabetes. Those variables that were categorical were specified as such. The Forward Stepwise Likelihood Ratio was used for this block of variables; only those that showed statistical significance were included in the model.

Results for the males, displayed in Table 21, showed that for males neither waist-to-hip ratio nor CRP contributed significantly to the model, while the Paffenbarger score was statistically significant with a relative risk of 0.91 [0.83 – 1.00]. This indicates that a

1000kcal/week increase in physical activity would be associated with a 9% decrease in IHD risk. Two additional covariates, systolic blood pressure and diastolic blood pressure were also significant at an alpha level of 0.05, with relative risks of 1.04 [1.02 – 1.05] and 0.96 [0.94 – 0.99], respectively. The relative risk for systolic blood pressure indicates that a one mmHg increase would be associated with a 4% increase in IHD risk, while the results for diastolic blood pressure suggest that a one mmHg increase would be associated with a 4% decrease in IHD risk.

Also seen in Table 21, when the potential additional covariates were included in the model for females, the waist-to-hip ratio remained significantly associated with the IHD outcome. The physical activity variable remained non-significant. The relative risk for CRP also remained statistically significant. The only additional covariate that was included in the model was age, with a relative risk of 1.04 [1.02 – 1.07].

Table 21 – Cox Proportional Hazards Regression model including waist-to-hip ratio, physical activity, inflammatory markers and additional covariates among males and females

Category	**Variable**	**RR [95% CI]**	
		Males	**Females**
Obesity indicator	Waist-to-hip ratio (0.1 unit)	1.28 [0.85 – 1.87]	1.23 [0.92 – 1.63]
Physical Activity	Paffenbarger score (1000 kcal/week)	0.91 [0.83 – 1.00]	0.99 [0.88 – 1.12]
Inflammatory marker	CRP (mg/dL)	0.98 [0.89 – 1.10]	1.13 [1.02 – 1.26]
Additional Covariates	Age	_____	1.04 [1.02 – 1.07]
	Systolic blood pressure	1.04 [1.02 – 1.05]	_____
	Diastolic blood pressure	0.96 [0.94 – 0.99]	_____

4.2.4 Supplementary analysis - Population Attributable Risk %

Calculation of the Population Attributable Risk % can be an important tool to assess the public health significance of key risk factors in the population. For each key risk factor in the study that had at least a borderline statistically significant relative risk in univariate analyses with IHD, this was done by subtracting the proportion of unexposed individuals who developed IHD from the total proportion of individuals who developed IHD, and then dividing by the total proportion of individuals who developed IHD. This number was then multiplied by 100 to obtain the Population Attributable Risk % (Oleckno, 2002). It is important to note, however, that when using this formula the assumption is made that each risk factor has a causal relationship with the outcome.

By examining the rates of incident IHD events for both normal (≤3.0mg/dL) and high (>3.0mg/dL, excluding those ≥10mg/dL) levels of CRP (Pearson et al, 2003), the Population Attributable Risk % for high CRP was determined. As with other analyses of inflammatory markers in this study, results differed greatly between males and females (Table 22). For females, results suggested that if everyone could lower their CRP level to 3.0 mg/dL or less, approximately 20% of incident IHD events could be eliminated. For males, the same analysis found that normalizing high CRP rates would only eliminate 3.0% of incident IHD events.

Higher magnitudes of Population Attributable Risk % for females compared to males were also seen when examining the obesity-IHD relationship and the physical activity-IHD relationship. Using the World Health Organization (2000) waist-to-hip ratio cut-off point of 0.85 for females, the Population Attributable Risk % of IHD due to

Table 22 – Estimation of the Population Attributable Risk % in development of IHD for risk factors with statistically significant relative risks

Variable	Cut-off point for exposure		Incidence rate in population	Incidence rate in unexposed group	PAR%
Waist-to-hip ratio	>0.85 (World Health Organization, 2000)	Females	58 / 463	22 / 218	19%
Paffenbarger score	<1000 kcal/week (Warburton et al, 2008)	Males	74 / 435	43 / 288	12%
CRP	>3.0 mg/L (Pearson et al, 2003)	Males	74 / 435	49 / 297	3.0%
	>3.0 mg/L (Pearson et al, 2003)	Females	58 / 464	30 / 298	20%

abdominal obesity was 19% for females. Due to lack of a statistically significant relative risk of IHD due to abdominal obesity for males, the Population Attributable Risk % for abdominal obesity in males could not be estimated. Similarly, because there was no significant relationship between physical activity and IHD for females, the Population Attributable Risk % for physical activity in females was not calculated, although it was determined that if all males expended at least 1000 kcal per week in leisure-time physical activity (Haennel & Lemire, 2002), approximately 12% of IHD in males could be eliminated.

Chapter 5

Discussion

5.1 Summary of study findings

This project examined the associations between several measures of body fat and abdominal fat, physical activity and inflammatory markers, and explored their associations with the development of IHD over a ten-year period. Based on our objectives, a number of key findings were noted and summarized here.

We found that waist-to-hip ratio was the fat-related variable with the strongest and most consistent relationship with IHD for women in univariate analyses. The same appeared true for males, although the results were not statistically significant. Of the inflammatory markers, CRP was the variable that demonstrated the strongest positive association with IHD in univariate analyses for men and women. Not surprisingly, waist-to-hip ratio was highly and significantly correlated with the other body fat and abdominal fat measures. However, body fat and abdominal fat-related variables showed much lower (but statistically significant) correlations with the inflammatory markers. When examined together in a multivariate model, waist-to-hip ratio and CRP were independently associated with IHD for women.

When we examined the univariate association between physical activity and IHD, a borderline statistically significant protective relationship was found for the males. Of the inflammatory markers, there was a small but statistically significant inverse correlation between physical activity and CRP for males and females. When examined together in a multivariate model, the relationship between physical activity and IHD for

the males did not change, remaining protective and borderline statistically significant. The CRP remained statistically significant in the model for women, but not for men.

In the final set of models, which included measures of abdominal fat, physical activity and inflammatory markers in the same model, all of the variables were in the expected direction. For men, however, physical activity was the only variable associated with IHD, though it was of borderline statistical significance. For women, waist-to-hip ratio and CRP were statistically significant and independently associated with IHD. Inflammation did not operate as a mediator in these associations in that there was no evidence to indicate that inflammation was in the pathway.

5.2 Discussion of Study Findings

There was clear evidence of a relationship between obesity and IHD for females, when using the waist-to-hip ratio as the obesity indicator. When using BMI as the obesity indicator, there were no statistically significant results detected. The analyses using the standardized Z-scores suggested that the waist-to-hip ratio was more important than BMI for males as well, but the associations were not statistically significant. The relative importance of the waist-to-hip ratio among both males and females points to the role of fat storage location in predicting cardiovascular risk, and suggests that an increase in fat storage around the abdominal region relative to the hip region is associated with an increased risk of IHD. The lack of significance of BMI as a predictor of IHD reinforces the idea that overall fat may not be as important for heart health as fat distribution. Other studies have reached similar conclusions (Welborn et al, 2003; Yusuf et al, 2005; Price et al, 2006; Winter et al, 2008; Sehested et al, 2010).

As predicted, and supported by the literature, the relationship between physical activity and IHD was in the protective direction, although the results were statistically significant for males only. Therefore, this study provided some evidence that an increase in the Paffenbarger score was associated with a decrease in IHD risk. Limitations associated with the use of self-report to measure physical activity may have diluted the true physical activity-IHD relationship. A recent systematic review examining the relationship between self-reported and directly measured physical activity found the correlations ranged from -0.71 to 0.96 (Prince et al, 2008). The authors concluded that although the self-reported and directly measured physical activity differed, there was no clear pattern that would allow researchers to correct for self-report bias (Prince et al, 2008).

The median Paffenbarger score of 1400 kcal/week among the individuals in this study is relatively high, and is above the suggested 1000kcal/week threshold that may be needed to provide protection against cardiovascular risk (Haennel & Lemire, 2002). In an average individual, approximately 1400 kilocalories per week could be expended by walking 175 city blocks, or approximately 23 kilometers. With a walking speed of 6 kilometers per hour, this expenditure of 1400 kcal per week translates into approximately four hours per week of walking, or 240 minutes.

Using the suggested threshold of 1000 kcal/week to classify individuals into physically active and inactive results in approximately 58% of the sample being classified as active and 32% being classified as inactive. In the larger sample from the 1995 Nova Scotia Health Survey, 39% of the individuals were classified as inactive based on their denying participation in any leisure time physical activity. Other sources have estimated

that in 1995, 55% of Canadian adults were physically inactive (Statistics Canada, 2011). This indicates that either the subsample in this study is much more active than the average Canadian, or that the physical activity measurements in our study may be falsely inflated, which may also help to explain the lack of statistically significant associations that were detected with this variable.

There was evidence of correlations between inflammation and obesity, and inflammation and physical activity. Both CRP and ICAM were associated with BMI and waist-to-hip ratio for both males and females, and ICAM was also associated with BMI and waist-to-hip ratio for females. C-Reactive Protein was also negatively associated with physical activity for males and females. C-Reactive Protein was the most important inflammatory marker for both males and females, although ICAM also showed some statistically significant results for the females.

While these sex-specific results for the inflammatory markers were unexpected, there has been research into the sex differences in CVD development and cardiovascular risk factors (Perez-Lopez et al, 2010). Previous research has shown that levels of ICAM differ by sex and age (Ponthieux et al, 2003), and may be related to concentrations of steroid hormones such as estrogen (Koh et al, 2001). A recent review of the related literature concluded that sex hormones including estradiol and androgens were important factors behind both the differences between males and females and the differences between pre- and post-menopausal females in rates of CVD and CVD risk factors (Perez-Lopez et al, 2010). This reinforces the importance of stratifying by sex when researching these topics. It also supports the importance of developing sex-specific clinical guidelines or cut-off points, as has been done for measurements like the waist-to-hip

ratio.

Examination of the relationships between the waist-to-hip ratio, CRP and IHD among females indicate that inflammatory markers do not appear to be a mediating factor in the relationship between body fat-related and abdominal fat-related variables and IHD. The relative risks for waist-to-hip ratio and CRP decreased minimally between their respective univariate models with IHD and their multivariate models with IHD but each remained significantly associated with IHD.

There was a borderline statistically significant univariate association between physical activity and IHD among the males, and there was also a statistically significant correlation between physical activity and CRP for the males. When CRP and physical activity were combined in a multivariate model with IHD, the relative risk of IHD due to physical activity remained unchanged, suggesting that CRP was not acting as a mediator.

The final model containing obesity, physical activity and inflammatory markers was intended to provide information about the relative importance of obesity and physical activity in the development of IHD. For the females, when the waist-to-hip ratio, physical activity and CRP were combined in a multivariate model, waist-to-hip ratio and CRP remained statistically significant. Similarly, in this model for males, physical activity remained borderline statistically significant. It is possible that the non-significant relationships seen (between physical activity and IHD for women, and obesity and IHD for men) may be an issue of sample size. Conversely, it may be that obesity is truly the risk factor driving the development of IHD for females, and physical activity is truly the key risk factor for males.

Markers of inflammation are present throughout atherogenesis, from initiation of

the fatty streak to growth of the atherosclerotic lesion, disruption of the lesion's cap, and finally rupture of the lesion (Pearson et al, 2003). There has been debate, however, about whether the inflammatory markers are truly risk factors (present in the causal pathway) or are risk markers (created as part of the disease process) (Pearson et al, 2003).

If inflammation is an independent risk factor for IHD, the question of its clinical usefulness naturally follows. Current recommendations issued by the Centers for Disease Control and the American Heart Association suggest that measurement of inflammatory markers as a screening tool at the population level should not be used in standard practice. They cite a lack of standardization, inconsistent conclusions in epidemiological studies, and insufficient evidence that this practice would be a significant improvement over current cardiovascular risk assessment methods (Pearson et al, 2003). However, the authors go on to say that measurement may be useful in specific clinical situations to provide more information about an individual's cardiovascular risk and to aid in decision-making regarding lifestyle or drug therapy (Pearson et al, 2003). They state that CRP is the marker of choice, and should always be used in combination with assessment of established risk factors, never as an alternative to them. This is reflected in the results of the current study, as CRP was the inflammatory marker most predictive of cardiovascular risk among males, and was also significant in females once those with extreme CRP levels were removed from the analysis.

The Canadian Cardiovascular Society reiterates the AHA guidelines in their 2009 publication Canadian Guidelines for the Diagnosis and Treatment of Dyslipidemia and Prevention of Cardiovascular Disease in the Adult (Genest et al, 2009). They recommend that inflammatory markers, and CRP specifically, should only be measured

in men over 50 and women over 60 who would be considered intermediate risk according to their Framingham Risk Score. The paper emphasizes that individuals of intermediate risk should be targeted because the measurement of CRP is only useful if its results will impact treatment decisions, and individuals with scores in the high-risk range would already qualify for treatment on this basis alone.

To provide information about the relative importance of obesity, physical activity and inflammation in IHD risk at the population level, the Population Attributable Risk was calculated. The results indicate that modifying any one of these variables at the population level could have an impact on the rates of IHD in Canada. Current recommendations presented in Canada's Guide to Physical Activity (Health Canada, 1998) state that adults should participate in at least 60 minutes of light activity each day, 30-60 minutes of moderate activity at least four times per week, or 20-30 minutes of vigorous activity at least four times per week. A recent press release from the Public Health Agency of Canada, however, has indicated that these guidelines will be revised in early 2011 to state that adults should be physically active for 150 minutes per week (Canadian Broadcasting Corporation, 2011). This would represent both a simplification and lowering of the guidelines. According to physical activity expert Mark Tremblay, the reasoning behind this change is that if the guidelines appear more achievable, then more members of the largely sedentary Canadian population will feel motivated to exercise (Canadian Broadcasting Corporation, 2011). Whether it is the Physical Activity Guidelines or an alternate public health message that finally causes a shift in the behaviour of Canadians, it is clear that something must change.

In conclusion, the results of this study suggest that obesity and inflammatory

markers each factor independently in the development of IHD for women, and it does not appear that inflammatory markers are mediators in the obesity-IHD relationship. For men, physical activity may be more important in the development of IHD.

5.3. Limitations, Strengths and Significance

5.3.1 Limitations

The main limiting factor in this study was sample size. After stratifying the sample by sex, the remaining numbers available for analysis were greatly reduced. Power calculations using the final data showed that for males, the available power was approximately 24%, while for females the available power was 37%. Although it is possible that additional conclusions could have been made with a larger sample size, the sample was still sufficient to detect several statistically significant associations. The associations that were found remain valid, however, due to low power, the lack of associations found remain inconclusive using this data.

Another limitation in this study is the measurement of body weight, physical activity level and inflammation at a single point in time. An assumption is made that these measurements continue to reflect an individual's situation, but it would be possible for them to change significantly. The fact that we measured only incident IHD, however, helps to mitigate this risk as individuals may be more likely to make significant changes to their lifestyle after experiencing major health events like acute myocardial infarction. Moreover, there is likely a lag time between exposures and the development of cardiovascular outcomes that would not be accounted for if ongoing measurements taken during follow-up were used.

As mentioned previously, there may be problems associated with the use of self-report in the measurement of physical activity. Not only is there the potential for individuals to misreport frequency or duration of physical activity, there is also the potential for great subjective difference in what individuals classify as light, moderate or

strenuous activity. If, as suggested by Prince et al (2008), there is no clear pattern to the measurement differences, then the true relationship between physical activity and inflammatory markers and physical activity and IHD has likely been diluted in this study.

Additionally, the physical activity questions focused largely on leisure-time physical activity, while some research has found that this makes up a relatively small proportion of individuals' total physical activity expenditure (Levine et al, 2007). Including data on physical activity during work, transportation and household chores would have allowed us to make a more accurate assessment of the relationship between physical activity and IHD. Conversely, if it is sedentariness that is more important than activity in determining the relationship with IHD, a measurement addressing inactivity would have been useful.

5.3.2 Strengths

This study has several strengths. The longitudinal design with a 10-year follow-up period helps strengthen the confidence in those relationships that were detected; very few studies have access to robust follow-up data such as this. Many other studies examining these topics use a cross-sectional design, which introduces concerns in determining cause-and-effect. The 1995 Nova Scotia Health Survey provided in-depth health and lifestyle data for a large and representative sample of males and females. There was a low loss-to-follow up rate, and the detailed information allowed for exploration of many additional covariates, several of which were associated with the outcome. Physical measurements, such as serum cholesterol, blood pressure, height, weight, waist and hip circumference and inflammatory markers, were collected by

specially trained research nurses, allowing for increased accuracy of the measurements.

Outcome data for this project was based on the objective endpoints of IHD-related hospitalizations and deaths. Compared to the American context, the organization of the Canadian healthcare system allows for accurate follow-up with subjects because citizens access the vast majority of acute care through provincially funded insurance. Although there may have been individuals in this sample who were not hospitalized for IHD during the follow-up but who did visit a primary care physician or emergency department for angina, these cases would likely have been significantly milder than those who were hospitalized or died from IHD. Therefore the potential exclusion of these mild IHD cases likely resulted in a more homogenous sample of outcome cases.

5.3.3 Significance

Obesity and participation in physical activity are already frequently targeted in clinical practice and public health messages. Other factors, such as serum cholesterol and triglycerides, are also regularly used by healthcare providers to assess cardiovascular risk. Current Canadian guidelines recommend measurement of CRP only in a specific subset of the population: males over 50 years and females over 60 years who have an intermediate cardiovascular risk according to their Framingham Risk Score (Genest et al, 2009). Future research into ethnic variation, differences between the values of males and females and the potential usefulness of other inflammatory biomarkers such as ICAM will provide additional information about their usefulness, and could result in modification of these guidelines.

If further research continues to support an independent relationship between

inflammation and IHD or CVD, measurement of inflammatory biomarkers in the clinical setting will provide additional information about individuals' cardiovascular risk, and in this way may help to prevent incident cardiovascular events from occurring.

5.3.4 Future Directions

The relationships between physical activity, obesity, inflammation and IHD are worthy of further investigation. Ideally, future studies would have access to more robust measures of physical activity and measures of body fat. Use of accelerometers as opposed to relying on self-report could provide actual data about duration and intensity of participants' movement, and would also provide information about the amount of time the participants are completely sedentary. Alternatively, physical fitness could be assessed using measures of oxygen consumption. The limitations of BMI could be overcome by using a direct measure of overall body fat, such as measurement of body fat percentage. Future studies using measurements like these would allow for more precise assessments of the associations between these important factors.

5.4 Conclusions

The World Health Organization estimated that in 2005, 1.6 billion people worldwide were overweight or obese, and forecasted that by 2015 this number would rise to approximately 2.3 billion (World Health Organization, 2010). Public health experts now consider the rise of obesity in Canada and around the world to be an epidemic (Finegood, 2009).

The current rate of overweight and obesity in Nova Scotia is particularly high, at 63% (Statistics Canada, 2010). Given the strong relationship between excess body weight and CVD, there are important health implications of this epidemic. If future research on inflammation continues to suggest that it is an independent risk factor for CVD, measurement of inflammatory markers in the clinical setting could be an important tool to identify those at risk of developing the disease. When taking into consideration issues of health care funding and resource allocation, the topic of cardiovascular risk factors is clearly an issue of importance for all members of society.

This project found evidence of relationships between abdominal obesity and IHD for women and physical inactivity and IHD for men. Inflammatory markers were also independently associated with obesity, physical activity and IHD, but there was no evidence that inflammation played a mediating role in the obesity-IHD relationship or physical activity-IHD relationship. Measurement of inflammatory markers has the potential to become a simple and objective tool that health care professionals could use to provide additional information about cardiovascular risk. Because health outcomes data continues to be collected for this cohort, future studies on the topic of obesity, physical activity, inflammation and IHD should be considered, as incorporating a longer follow-up

period into the analysis could potentially increase the power available to explore these important and complex relationships.

References

Aadahl, M., von Huth Smith, L., Pisinger, C., Toft, U. N., Glmer, C., Borch-Johnsen, K., et al. (2009). Five-year change in physical activity is associated with changes in cardiovascular disease risk factors: The Inter99 study. *Preventive Medicine, 48*(4), 326-331.

Agapakis, D., Tsantilas, D., Psarris, P., Massa, E., Kotsaftis, P., Tziomalos, K., et al. (2010). Coagulation and inflammation biomarkers may help predict the severity of community-acquired pneumonia. *Respirology, 15*(5), 796-803.

Agrawal, V., Krause, K., Chengelis, D., Zalesin, K., Rocher, L., & McCullough, P. (2009). Relation between degree of weight loss after bariatric surgery and reduction in albuminuria and C-reactive protein. *Surgery for Obesity and Related Diseases, 5*(1), 20-26.

Altieri, A., Tavani, A., Gallus, S., & La Vecchia, C. (2004). Occupational and leisure time physical activity and the risk of nonfatal acute myocardial infarction in Italy. *Annals of Epidemiology, 14*(7), 461.

Andersson, O. K., Almgren, T., Persson, B., Samuelsson, O., Hedner, T., & Wilhelmsen, L. (1998). Survival in treated hypertension: Follow up study after two decades. *BMJ.British Medical Journal, 317*(7152), 167-171.

Arikawa, A., Thomas, W., Schmitz, K., & Kurzer, M. (2010). Sixteen weeks of exercise reduces C-reactive protein levels in young women. *Medicine and Science in Sports and Exercise,*

Armstrong, T., & Bull, F. (2006). Development of the world health organization global physical activity questionnaire. *Journal of Public Health, 14*(2), 66-70.

Arnlv, J., Ingelsson, E., Sundstrm, J., & Lind, L. (2010). Impact of body mass index and the metabolic syndrome on the risk of cardiovascular disease and death in middle-aged men. *Circulation, 121*(2), 230-236.

Baena-Dez, J., Byram, A., Grau, M., Gmez-Fernndez, C., Vidal-Solsona, M., Ledesma-Ulloa, G., et al. (2010). Obesity is an independent risk factor for heart failure: Zona franca cohort study. *Clinical Cardiology, 33*(12), 760-764.

Birman-Deych, E., Waterman, A. D., Yan, Y., Nilasena, D. S., Radford, M., & Brian, G. (2005). Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. *Medical Care, 43*(5), 480-485.

Buckley, D., Fu, R., Freeman, M., Rogers, K., & Helfand, M. (2009). C-reactive protein as a risk factor for coronary heart disease: A systematic review and meta-analyses

for the U.S. preventive services task force. *Annals of Internal Medicine, 151*(7), 483-495.

Canadian Broadcasting Corporation. (2011). *Fitness targets to be lowered for Canadians.* Retrieved 01/15, 2011, from http://www.cbc.ca/health/story/2010/12/31/exercise-fitness-guidelines-canada-weighs-in.html#socialcomments

Church, T. S., LaMonte, M. J., Barlow, C. E., & Blair, S. N. (2005). Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. *Archives of Internal Medicine, 165*, 2114-2120.

Colley, R. C., Garriguet, D., Janssen, I., Craig, C. L., Clarke, J., & Tremblay, M. S. (2011). Physical activity of Canadian adults: Accelerometer results from the 2007 to 2009 Canadian health measures survey. *Health Reports, 22*(1).

Compher, C., & Badellino, K. O. (2008). Obesity and inflammation: Lessons from bariatric surgery. *JPEN, Journal of Parenteral and Enteral Nutrition, 32*(6), 645.

Cushman, M., Arnold, A. M., Psaty, B. M., Manolio, T. A., Kuller, L. H., Burke, G. L., et al. (2005). C-reactive protein and the 10-year incidence of coronary heart disease in older men and women: The cardiovascular health study. *Circulation, 112*(1), 25.

Davidson, K., Schwartz, J., Kirkland, S., Mostofsky, E., Fink, D., Guernsey, D., et al. (2009). Relation of inflammation to depression and incident coronary heart disease (from the Canadian Nova Scotia Health Survey [NSHS95] prospective population study). *The American Journal of Cardiology, 103*(6), 755-761.

den Hertog, H. M., van Rossum, J. A., van der Worp, H. B., van Gemert, H. M. A., de Jonge, R., Koudstaal, P. J., et al. (2009). C-reactive protein in the very early phase of acute ischemic stroke: Association with poor outcome and death. *Journal of Neurology,* [Epud ahead of print]

Finegood, D. (2009). Canada in context: Challenging our epidemics of obesity and obesity-related chronic diseases. *Health Reports, 20*(4), 9-10.

Genest, J., McPherson, R., Frohlich, J., Anderson, T., Campbell, N., Carpentier, A., et al. (2009). 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. *The Canadian Journal of Cardiology, 25*(10), 567-579.

Haennel, R. G., & Lemire, F. (2002). Physical activity to prevent cardiovascular disease. how much is enough? *Canadian Family Physician, 48*, 65.

Hamer, M., & Chida, Y. (2008). Walking and primary prevention: A meta-analysis of prospective cohort studies. *British Journal of Sports Medicine, 42*(4), 238.

Haskell, W., Lee, I., Pate, R., Powell, K., Blair, S., Franklin, B., et al. (2007). Physical activity and public health: Updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation, 116*(9), 1081-1093.

Health Canada. (1998). *Canada's guide to physical activity*. Retrieved 01/15, 2011, from http://www.hc-sc.gc.ca/hl-vs/physactiv/index-eng.php

Health Canada. (2003). *Canadian guidelines for body weight classification in adults*. Ottawa: Health Canada Publications Centre.

Heart and Stroke Foundation of Canada. (2006). *Overweight, obesity, heart disease and stroke.* Retrieved 03/13, 2008, from http://www.heartandstroke.com/site/c.ikIQLcMWJtE/b.3799193/k.C2EF/Overweight_obesity_and_heart_disease_and_stroke.htm

Hubert, H. B., Feinleib, M., McNamara, P. M., & Castelli, W. P. (1983). Obesity as an independent risk factor for cardiovascular disease: A 26-year follow-up of participants in the framingham heart study. *Circulation, 67*(5), 968.

Ishikawa, S., Kayaba, K., Gotoh, T., Nakamura, Y., Kario, K., Ito, Y., et al. (2007). Comparison of C-reactive protein levels between serum and plasma samples on long-term frozen storage after a 13.8 year interval: The JMS cohort study. *Journal of Epidemiology, 17*(4), 120.

Juneau, C., & Potvin, L. (2010). Trends in leisure-, transport-, and work-related physical activity in Canada 1994-2005. *Preventive Medicine, 51*(5), 384-386.

Katzmarzyk, P., Church, T., Craig, C., & Bouchard, C. (2009). Sitting time and mortality from all causes, cardiovascular disease, and cancer. *Medicine and Science in Sports and Exercise, 41*(5), 998-1005.

Kodama, S., Saito, K., Tanaka, S., Maki, M., Yachi, Y., Asumi, M., et al. (2009). Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. *JAMA (Chicago, Ill.), 301*(19), 2024-2035.

Koh, K. K., Jin, D. K., Yang, S. H., Lee, S. K., Hwang, H. Y., Kang, M. H., et al. (2001). Vascular effects of synthetic or natural progestagen combined with conjugated equine estrogen in healthy postmenopausal women. *Circulation, 103*(15), 1961-1966.

Lee, D., Chiu, M., Manuel, D., Tu, K., Wang, X., Austin, P., et al. (2009). Trends in risk factors for cardiovascular disease in Canada: Temporal, socio-demographic and geographic factors. *Canadian Medical Association.Journal CMAJ, 181*(3-4), E55-E66.

Levine, J. A. (2007). Nonexercise activity thermogenesis--liberating the life-force. *Journal of Internal Medicine, 262*(3), 273-287.

Li, T. Y., Rana, J. S., Manson, J. E., Willett, W. C., Stampfer, M. J., Colditz, G. A., et al. (2006). Obesity as compared with physical activity in predicting risk of coronary heart disease in women. *Circulation, 113*(4), 499.

Marcinkowski, M., Czarnecka, D., Jastrzebski, D. F., & Kawecka-Jaszcz, K. (2007). Inflammatory markers 10 weeks after myocardial infarction predict future cardiovascular events. *Cardiology Journal, 14*(1), 50.

Mora, S., Cook, N., Buring, J. E., Ridker, P. M., & Lee, I. M. (2007). Physical activity and reduced risk of cardiovascular events: Potential mediating mechanisms. *Circulation, 116*(19), 2110.

National Cancer Institute. (2010). *Walking & bicycling related items from physical activity questionnaires.* Retrieved from http://appliedresearch.cancer.gov/tools/paq/reflist.html

Nocon, M., Hiemann, T., Muller-Riemenschneider, F., Thalau, F., Roll, S., & Willich, S. N. (2008). Association of physical activity with all-cause and cardiovascular mortality: A systematic review and meta-analysis. *European Journal of Cardiovascular Prevention and Rehabilitation, 15*(3), 239.

Nova Scotia Department of Health, & Heart Health Nova Scotia. (1996). *1995 Nova Scotia Health Survey: Executive summary* (Executive Summary. Nova Scotia: Communications Nova Scotia.

Nusselder, W., Franco, O., Peeters, A., & Mackenbach, J. (2009). Living healthier for longer: Comparative effects of three heart-healthy behaviors on life expectancy with and without cardiovascular disease. *BMC Public Health, 9*, 487-487.

Obesity: Preventing and managing the global epidemic. Report of a WHO consultation.(2000). *World Health Organization Technical Report Series, 894*, i-xii, 1.

Oleckno, W. A. (2002). Essential epidemiology. Long Grove, IL: Waveland Press Inc.

Orsini, N., Bellocco, R., Bottai, M., Pagano, M., Michaelsson, K., & Wolk, A. (2008). Combined effects of obesity and physical activity in predicting mortality among men. *Journal of Internal Medicine, 264*(5), 442-451.

Panagiotakos, D., Pitsavos, C., Chrysohoou, C., Skoumas, I., & Stefanadis, C. (2008). Five-year incidence of cardiovascular disease and its predictors in Greece: The ATTICA study. *Vascular Medicine, 13*(2), 113-121.

Pardo, S. M. C., De Laet, C., Nusselder, W. J., Mamun, A. A., & Peeters, A. (2006). Adult obesity and number of years lived with and without cardiovascular disease. *Obesity, 14*(7), 1264.

Pearson, T. A., Mensah, G. A., Alexander, R. W., Anderson, J. L., Cannon, R. O., Criqui, M., et al. (2003). Markers of inflammation and cardiovascular disease: Application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation, 107*(3), 499.

Pitsavos, C., Panagiotakos, D. B., Tzima, N., Lentzas, Y., Chrysohoou, C., Das, U. N., et al. (2007). Diet, exercise, and C-reactive protein levels in people with abdominal obesity: The ATTICA epidemiological study. *Angiology, 58*(2), 225.

Ponthieux, A., Herbeth, B., Droesch, S., Lambert, D., & Visvikis, S. (2003). Age- and sex-related reference values for serum adhesion molecule concentrations in healthy individuals: Intercellular adhesion molecule-1 and E-, P-, and L-selectin. *Clinical Chemistry, 49*(9), 1544-1546.

Price, G., Uauy, R., Breeze, E., Bulpitt, C., & Fletcher, A. (2006). Weight, shape, and mortality risk in older persons: Elevated waist-hip ratio, not high body mass index, is associated with a greater risk of death. *The American Journal of Clinical Nutrition, 84*(2), 449-460.

Prince, S., Adamo, K., Hamel, M., Hardt, J., Gorber, S., & Tremblay, M. (2008). A comparison of direct versus self-report measures for assessing physical activity in adults: A systematic review. *The International Journal of Behavioral Nutrition and Physical Activity, 5*, 56-56.

Prizment, A., Anderson, K., Visvanathan, K., & Folsom, A. (2011). Association of inflammatory markers with colorectal cancer incidence in the atherosclerosis risk in communities study. *Cancer Epidemiology, Biomarkers Prevention,*

Probert, A. W., Tremblay, M. S., & Connor Gorber, S. (2008). Desk potatoes: The importance of occupational physical activity on health. *Canadian Journal of Public Health, 99*(4), 311-318.

Public Health Agency of Canada. (2007). *Strategic plan 2007-2012: Where we're going.* Retrieved March/13, 2008, from http://www.phac-aspc.gc.ca/publicat/2007/sp-ps/SPPS-06a-eng.html

Public Health Agency of Canada. (2009). *Minimizing the risks of cardiovascular disease.* Retrieved 04/18, 2009, from http://www.phac-aspc.gc.ca/cd-mc/cvd-mcv/risk-risques-eng.php

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Thomas, R. J., Collazo-Clavell, M.

L., Korinek, J., et al. (2008). Accuracy of body mass index in diagnosing obesity in the adult general population. *International Journal of Obesity, 32*(6), 959-966.

Sehested, T. S. G., Hansen, T., Olsen, M., Abildstrm, S., Rasmussen, S., Ibsen, H., et al. (2010). Measures of overweight and obesity and risk of cardiovascular disease: A population-based study. *European Journal of Cardiovascular Prevention and Rehabilitation, 17*(4), 486-490.

Shen, H., Zhang, N., Zhang, X., & Ji, W. (2009). C-reactive protein levels after 4 types of arthroplasty. *Acta Orthopaedica, 80*(3), 330-333.

Smolderen, K., Bell, A., Lei, Y., Cohen, E., Steg, P. G., Bhatt, D., et al. (2010). One-year costs associated with cardiovascular disease in canada: Insights from the REduction of Atherothrombosis for Continued Health (REACH) registry. *The Canadian Journal of Cardiology, 26*(8), 297-305.

Sofi, F., Capalbo, A., Cesari, F., Abbate, R., & Gensini, G. (2008). Physical activity during leisure time and primary prevention of coronary heart disease: An updated meta-analysis of cohort studies. *European Journal of Cardiovascular Prevention and Rehabilitation, 15*(3), 247-257.

Statistics Canada. (2010). *Canadian socioeconomic information management system.* Retrieved 04/18, 2010, from cansim2.statcan.ca

Stehno-Bittel, L. (2008). Intricacies of fat. *Physical Therapy, 88*(11), 1265-1278.

Sui, X., LaMonte, J., Laditka, J. N., Hardin, J. W., Chase, N., Hooker, S. P., et al. (2007). Cardiorespiratory fitness and adiposity as mortality predictors in older adults. *Journal of the American Medical Association, 298*(21), 2507-2516. Retrieved from http://jama.ama-assn.org.ezproxy.library.dal.ca/cgi/content/full/298/21/2507

Tjepkema, M. (2005). *Nutrition: Findings from the Canadian Community Health Survey*. Ottawa: Statistics Canada.

Tseng, C. (2008). Waist-to-height ratio and coronary artery disease in Taiwanese type 2 diabetic patients. *Obesity, 16*(12), 2754-2759.

van Uffelen, J. G. Z., Wong, J., Chau, J., van der Ploeg, H., Riphagen, I., Gilson, N., et al. (2010). Occupational sitting and health risks: A systematic review. *American Journal of Preventive Medicine, 39*(4), 379-388.

Wee, C., Mukamal, K., Huang, A., Davis, R., McCarthy, E., & Mittleman, M. (2008). Obesity and C-reactive protein levels among white, black, and hispanic US adults. *Obesity, 16*(4), 875-880.

Weinstein, A., Sesso, H., Lee, I., Rexrode, K., Cook, N., Manson, J., et al. (2008). The

joint effects of physical activity and body mass index on coronary heart disease risk in women. *Archives of Internal Medicine, 168*(8), 884-890.

Welborn, T., Dhaliwal, S., & Bennett, S. (2003). Waist-hip ratio is the dominant risk factor predicting cardiovascular death in australia. *Medical Journal of Australia, 179*(11-12), 580-585.

Wing, R. R., Jakicic, J., Neiberg, R., Lang, W., Blair, S. N., Cooper, L., et al. (2007). Fitness, fatness, and cardiovascular risk factors in type 2 diabetes: Look ahead study. *Medicine and Science in Sports and Exercise, 39*(12), 2107.

Winter, Y., Rohrmann, S., Linseisen, J., Lanczik, O., Ringleb, P., Hebebrand, J., et al. (2008). Contribution of obesity and abdominal fat mass to risk of stroke and transient ischemic attacks. *Stroke, 39*(12), 3145-3151.

World Health Organization. (2000). *Obesity: Preventing and managing the global epidemic. report of a WHO consultation.* No. 894). Geneva: The Organization.

World Health Organization. (2010). *Fact sheet: Overweight and obesity* No. 311. World Health Organization.

Xie, J., Wu, E., Zheng, Z., Sullivan, P., Zhan, L., & Labarthe, D. (2008). Patient-reported health status in coronary heart disease in the United States: Age, sex, racial, and ethnic differences. *Circulation, 118*(5), 491-497.

Yusuf, S., Hawken, S., Ounpuu, S., Bautista, L., Franzosi, M. G., Commerford, P., et al. (2005). Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: A case-control study. *Lancet, 366*(9497), 1640.