

**THE ABILITY OF THE ‘SCORE’ RISK MODEL
TO PREDICT 10-YEAR CARDIOVASCULAR DISEASE MORTALITY:
CANADIAN HEART HEALTH SURVEYS (CHHS) FOLLOW-UP STUDY
AS AN EXAMPLE**

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By

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“Prediction is difficult, especially when dealing with the future”

.....Danish Proverb

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ABSTRACT

The purpose of this study is to evaluate the predictive accuracy of the SCORE (Systematic COronary Risk Evaluation) risk prediction model to predict the risk of 10-year cardiovascular disease (CVD) mortality in Canadian Heart Health Surveys (CHHS) Follow-up Study population.

The study used data from The Canadian Heart Health Surveys (CHHS) Follow-up Study which is a linked dataset of Canadian Heart Health Surveys (1986-1992), a baseline cross-sectional complex surveys and Canadian Mortality Database by Statistics Canada. SCORE CVD risk prediction models for both high- and low-risk regions were used to calculate the predicted deaths from cardiovascular disease over a period of 10-year for both men and women aged 40-69 years with no previous history of cardiovascular disease. The predicted number of deaths was compared with observed CVD deaths (stratified by age and sex) in the CHHS Follow-up Study population. .

Over a period of 10-year, the observed absolute risk of cardiovascular death in CHHS population was found to be 1.9% (95% CI: 1.87, 1.92) in male and 0.9% (95% CI: 0.87, 0.90) in female. By using SCORE high-risk model, the observed vs. expected death (O/E) ratio was found to be 0.54, 0.34, 0.49 in men and 0.55, 0.52, 0.50 in women respectively for the age group 40-49, 50-59 and 60-69 years. The SCORE low- model predicted O/E ratio of 1.06, 0.63, 0.87 in men and 0.88, 0.80, 0.75 in women respectively for age group 40-49, 50-59, and 60-69 years. Twenty-eight percent of males and seven percent of females were identified to have a risk of 5% or more of having a fatal CVD event within next 10 years by the SCORE high-risk model and the same was found to be in 12% of males and 5% of females respectively by the SCORE low-risk model.

Application of the original SCORE models for high- and low-risk regions in Canadian Heart Health Survey Follow-up Study data has resulted in over prediction of the number of CVD deaths. SCORE low-risk model performed better than the high-risk version. Recalibration of SCORE risk prediction model is suggested if it is considered to be used in Canada.

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Shaikh Ohi Mohammad Tantanah, my youngest brother, and
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*If tears could build a stairway, and memories a lane
I'd walk right up to heaven and bring you two back again..... (Collected¹)*

¹ Collected from <http://www.scrapbook.com/poems/doc/13433.html>

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ABBREVIATION

AMI	Acute Myocardial Infarction
AUC	Area Under Curve
CHD	Coronary Heart Disease
CHHS	Canadian Heart Health Surveys
CUORE	An Italian longitudinal study
CVD	Cardiovascular Disease
FINRISK	Finnish population survey on risk factors on chronic, non-communicable diseases
FRS	Framingham Risk Score
HAPPIEE	The Health, Alcohol, and Psychosocial factors in Eastern Europe study
HDL	High Density Lipoprotein
ICD-9	International Classification of Diseases 9
ICD-10	International Classification of Diseases and Related Health Problems, (10th edition)
IHD	Ishcaemic Heart Disease
KORA	Cooperative Health Research in the Region Augsburg (a German regional research platform)
MONICA	MONItoring of trends and determinants in CArdiovascular disease
PROCAM	PROspective CArdiovascular Munster study
QRISK	A new CVD risk score based on QResearch database
SBP	Systolic Blood Pressure
SCORE	Systematic COronary Risk Evaluation
SHIP	Study of Health in Pomerania
VHM&PP	Vorarlberg Health Monitoring and Promotion Programme

CHAPTER 01: INTRODUCTION

1.1 Rationale

The Cardiovascular diseases (CVDs) represented 31% of all global deaths in 2012 by taking lives of almost 17.5 million people worldwide; hence established itself as the world's number one cause of death (1). Statistics Canada identified CVDs (both heart disease and cerebrovascular disease) as the leading cause of death in 2011 for both men and women in Canada (2). Cardiovascular disease alone costs about CAD \$ 22.2 billion in 2000 making it as the 'disease' of the second leading economic burden in Canada (3, 4).

Though CVDs comprise a group of disorders, atherosclerotic variety is the principal cause of death – heart attack and stroke were responsible for around 78% of all CVDs deaths worldwide in 2008 (5). It is evidenced that the development of CVDs is strongly related to multiple number of risk factors and identifying these risk factors is one of the greatest achievements of 20th-century epidemiology (6). Research have shown that patients with these risk factors are at substantially increased risk of developing CVDs and control trials have demonstrated that correction of predisposing risk factors by therapy such as dyslipidemia and hypertension does reduce the risk of developing CVD² events (7)

The focus of CVD management has observed a change over the past decade – a shift from relative risk to targeting the incidence of events of CVD, i.e., the absolute risk of the disease and the newer CVD management guidelines prioritizing treating patients with high absolute risk (8). It is an established fact that CVD is the constellation of several risk factors which may interact to greatly increase the risk of the disease; thus any treatment approach focusing on managing any

² CVD (Cardiovascular disease) and CVDs (Cardiovascular diseases) have been used interchangeably

single risk factors might result in ill-chosen decisions (9). The importance of using multivariable risk assessment as a key component of primary prevention program for CVDs both at an individual and at the population level is recognised and the current CVD treatment guidelines emphasized the use of risk estimation by taking into consideration a group of risk factors before making clinical management decisions (10, 11).

CVD risk prediction models are the statistical model that helps quantifying the risk of individual's probability of developing CVDs by forming a single prediction equation and is developed from prospective cohort studies as risk predictions are inherently longitudinal in nature (66). Framingham Risk Score (FRS) is the pioneer of CVD risk prediction models and has been widely researched around the world (12). The Framingham risk prediction model found to be mostly overestimating absolute coronary risk in European population (13, 14) and in some situations; it performed in close agreement with other risk prediction models (15). Thus, the generalization of the Framingham risk equation to the population of different countries and ethnic origins is a matter of concern. Given the situation in European context led to the development of SCORE (**S**ystematic **C**oronary **R**isk **E**valuation) risk prediction model (16, 59). The SCORE risk prediction model is developed based on the risk factors and CVD mortality data from 12 European cohort studies and it predicts the 10-year absolute risk of a fatal atherosclerotic CVD event (16). High and low-risk versions of the SCORE model has been developed based on the local CVD risk status of the population in Europe, so that it can be used targeting the appropriate population group (16). SCORE model has been adopted to use by the Joint European Task Force on cardiovascular prevention in 2003 (11) and has been evaluated in different European countries which showed varied results (either overestimation, underestimation or adequate prediction) across the region (17, 18, 19, 20, 21, 22).

The Framingham model has been endorsed by the Canadian Cardiovascular Society (CCS) Position Statement for the diagnosis and treatment of Dyslipidemias (23). However, Cooney et al in 2009 stated the importance of a clearly defined outcome variable of any risk score equation as that prevent coding difficulties when the function is applied to an external population (9). Framingham Risk Equation considered both hard (death) and soft outcomes (coronary insufficiency, an onset of angina etc.) for its different versions (52, 54, 62). On the contrary, the SCORE risk model considered only the CVD fatal events as its outcome which is easy to replicate in a different context; most of the countries usually have national cause-specific mortality data even if they do not have cohort study on cardiovascular disease (16).

Canada has observed a gradual decline in death from the cardiovascular disease since the middle of past century (24). The risk of cardiovascular disease varies greatly across people of different ethnic groups in Canada (25, 26) and there remains a significant regional variation in age-standardized CVD and Ischemic Heart Disease (IHD) mortality rate in Canada (27). Baseline rate of CVD in different geographic regions plays an important role to the accurate prediction of CVD (28). To our knowledge, no Canadian risk prediction model is currently available (29) to predict CVD risk nor is enough evidence available regarding the performance of other foreign models in a local context which urges the priority to minimize the existing knowledge gap. SCORE is considered as a probable risk estimation model that might be appropriate for Canada (29).

Canadian Heart Health Surveys Follow-up Study is a longitudinal follow-up of the Canadian Heart Health Surveys (CHHS) which has been linked to the Canadian Mortality Database (CMBD) (110, 111). This linked database provides an excellent opportunity to evaluate the performance of SCORE risk model in Canadian context hence generating new knowledge in this

field. Thus the aim of this study is to evaluate the predictive accuracy of ‘SCORE risk function for both the ‘high- and low-risk region’ by using the Canadian Heart Health Surveys Follow-up Study population. The current study will address the following research question and the objectives:

1.2 Research question

- How well does the SCORE CVD risk prediction model predict 10-year cardiovascular disease mortality in Canadian Heart Health Surveys (CHHS) Follow-up Study?

1.3 Objectives

- To calculate the standardized all-cause and cardiovascular mortality of the CHHS study population
- To estimate the 10-year risk of having fatal cardiovascular events in CHHS population by using both the SCORE high and low-risk models
- To assess how closely the predicted risk of having cardiovascular death approaches the actual death observed in CHHS population

2.1 Definition of cardiovascular disease

The Public Health Agency of Canada has defined “Cardiovascular diseases (CVDs) as a term that refers to more than one disease of the circulatory system including diseases of the heart and blood vessels, whether the blood vessels are affecting the lungs, the brain, kidneys or other parts of the body” (4). Cardiovascular disease has been broadly classified into two main categories by the World Health Organization which is described below (5):

- (i) **CVDs due to atherosclerosis:** Ischemic heart disease or coronary artery disease (e.g. heart attack), cerebrovascular disease (e.g. stroke), and diseases of the aorta and arteries, including hypertension and peripheral vascular disease, and
- (ii) **Other CVDs:** Congenital heart disease, Rheumatic heart disease, Cardiomyopathies and Cardiac arrhythmias. (5)

Atherosclerosis is a complex pathological process in which fatty material and cholesterol get deposited in the wall of the blood vessels gradually over many years of time due to the overall effect of the several CVD risk factors and it seldom results from a single risk factor (5, 47). Atherosclerosis causes narrowing of blood vessels making it harder for blood to flow through and usually progressed to an advance stage by the time symptoms occur (5). The atherosclerotic variety of CVD, especially coronary heart disease remains the predominant cause of death worldwide (5, 60).

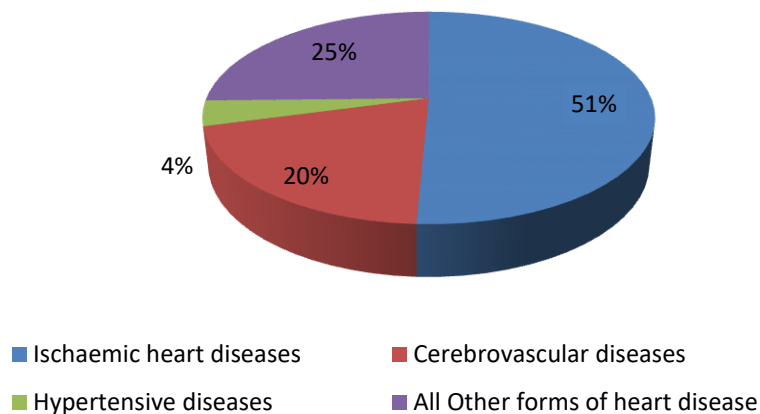
2.2 Epidemiology of cardiovascular disease

Cardiovascular diseases (CVDs), being the leading cause of global death claimed around 7.4 million and 6.7 million lives in 2012 due to coronary heart disease and stroke respectively (1).

Ischemic Heart Disease (IHD³) and cerebrovascular disease are the predominant types of cardiovascular diseases (5, 112). According to World Health Organization 2011 report, death due IHD represents 46% of total CVD deaths in male and 38% of that in the female (5). Similarly, cerebrovascular disease constitutes 34% and 37% of total CVD deaths in male and female respectively (5).

Statistics Canada Health Report 2005 identified diseases of the circulatory system as high burden diseases and the leading cause of death in Canada which accounted for 34% of total deaths in people older than twenty in 2002 (30).

Figure 2.1 Distribution of CVD deaths in Canada 2011



Source: Table 102-0529, Statistics Canada 2015

As shown in Figure 2.1, ischemic heart disease (IHD) and cerebrovascular disease together accounted for 71% all cardiovascular deaths in Canada in 2011 (31). In Canada, an estimated 57% of CVD deaths were due to ischaemic heart disease in male and 44% of the same was reported in the female in 2011 (31). Deaths due to cerebrovascular disease account for about 17% and 23% of all CVD deaths in male and female respectively in 2011 (31). The economic

³ IHD is the result of Coronary artery disease where oxygen supply to the heart muscle is compromised

burden of cardiovascular disease is also very high in Canada. According to the Public Health Agency of Canada report 2009 the direct (*hospital care, drugs, physician care, other institutional care, etc.*) and indirect cost (*relating to mortality, and short and long term disability*) estimated for the cardiovascular disease was CAD \$ 22.2 billion in 2000, second leading economic burdened disease in Canada (3). Canada has observed a decline in CVD deaths; between 1950 and 1999 the death rates from CVD dropped from 702 per 100,000 to 288 per 100,000 men, and from 562 per 100,000 to 175 per 100,000 women as stated by Manuel DG and colleagues (24). Standardized mortality rates for stroke and heart disease showed the largest decrease amongst all 10 leading cause of deaths over the period from 2000 to 2011 in Canada (32). Death from heart disease showed a 41.2% decline and that of stroke showed a 40.1% decline respectively, yet CVD remains the second leading cause of death in Canada (32).

2.3 Risk factors for cardiovascular diseases

Cardiovascular diseases are chronic conditions and multifactorial in nature (11). The Framingham Heart study (www.framinghamheartstudy.org) provided ample of opportunities for decades of observation to identify the risk factors of major atherosclerotic CVDs which comprise the major portion of the disease (12). It is evidenced that majority of cardiovascular diseases are caused by risk factors which can be controlled, treated or modified (also known as modifiable risk factors); such as high blood pressure (33), diabetes (34), increased total cholesterol (37), overweight/obesity (35), smoking (38), harmful use of alcohol (39), lack of physical activity (36), and stress (40). However, age, gender, and positive family history are identified as non-modifiable (that can't be controlled) CVD risk factors (41). The Global INTERHEART case-control study has demonstrated that nine easily measurable risk factors (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits,

vegetables, & alcohol, and regular physical activity) are associated with more than 90% of the risk of an acute Myocardial Infarction (AMI) which are consistent across all geographic regions, and ethnic groups of the world, men and women, and young and old (42).

2.4 Prevention strategy of cardiovascular diseases

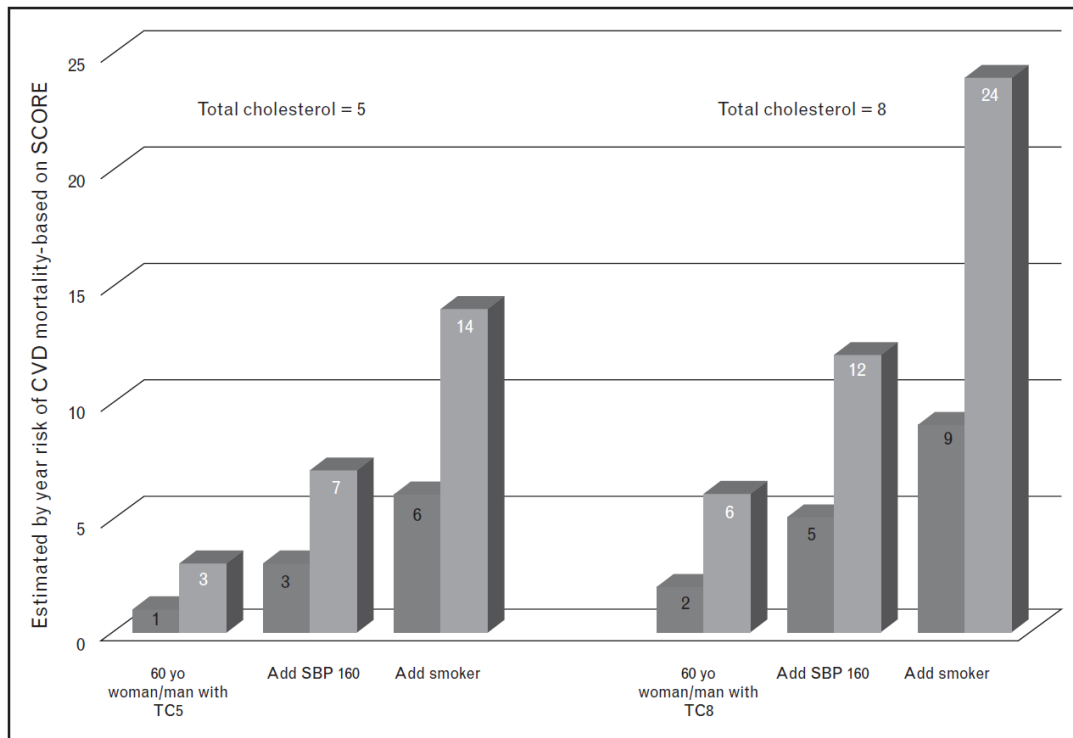
There are two widely recognized strategies for prevention of cardiovascular diseases – (i) the high-risk strategy, and (ii) population-based strategy (43). The high-risk strategy targets individuals with high-risk of disease and gives treatment – the way clinicians practice; and the population strategy focuses on reducing the incidence of the disease by shifting the risk factor distribution of the entire population in a favorable direction – e.g. community intervention for a particular condition (43). Rose 1981 drew attention to prevention paradox meaning a measure that brings large benefit to the community offers little to each participating individual (44). Rose stated that these two strategies have their disadvantages and are not in a competition, but identifying the causes of incidence and controlling those should be prioritized (45). Emberson et al. 2004 estimated the effectiveness of both the strategies and ‘high-risk’ strategy was found to be potentially effective but needed to be used widely to have substantial effect on CVD; in contrast, modest downwards shifts in the population distribution of total cholesterol and systolic blood pressure was found to marked expected reduction in major CVD (46). However, both the strategies are complementary to each other to address the increasing rates of CVD in developing countries but also to continue the CVD declining trend in developed countries (43). High-risk strategy is the basis of the multivariable risk prediction tools which are recommended by regulatory bodies and these enable clinicians to more precise identification of those people who are at elevated risk of developing CVDs (48).

2.5 Risk assessment in cardiovascular disease

During the eighties and nineties, clinical recommendation for cardiovascular disease management was focused primarily on management of a single risk factor, particularly hypertension and raised cholesterol level and separate treatment guidelines were available for managing each risk factor (8). But atherosclerosis is responsible for the majority of CVDs, and atherosclerosis is a combined result of a constellation of several risk factors rarely the outcome of a single risk factor, e.g. familial hyperlipidemia (47). Individuals' lifestyles and the presence of modifiable risk factors are strongly related to the mass occurrence of CVD; modification of these risk factors unequivocally showed to reduce mortality and morbidity, e.g. cessation of smoking and control of hypertension and blood cholesterol (9, 11).

The presence of atherosclerotic CVDs, or diabetes, or markedly elevated single risk factor in individuals are established as belong to a high-risk group of CVD (48). Framingham Heart study showed that the major risk factors for CVD are additive in predictive power (52). Thus, a person's risk of having CVD can be calculated by summing up the risk imparted by each of the major risk factors whichever he/she is having (53). An individual with modestly elevated level of several risk factors have a higher chance of having fatal CVD event than a person with markedly elevated single risk factor because of the risk factors interact, sometimes multiplicatively (47). Figure 2.2 has been taken from Cooney et al. 2011 publication which indicates how the risk of having fatal CVD event varies between individuals at a different combination of CVD risk factors (48).

Figure 2.2 Ten-year risk of CVD mortality (calculated using SCORE*) for men and women with total cholesterol levels of 5mmol/L and 8mmol/L and varying level of other risk factors



* SCORE (Systematic Coronary Risk Evaluation)

Source: Cooney et al 2011

Over the past few decades, a remarkable change has occurred in the management of cardiovascular disease, a movement from recommendations based on relative risk to recommendations based on absolute risk (8). Absolute risk means the probability of developing a certain event (disease) which gives a useful means of risk communication with patients (49). To cite an example, if a patient is estimated to have a 10-years CVD risk of 8% - the appropriate interpretation would be to say if 100 individuals have similar level of risk factors as those of the patient, 8 will experience a CVD event in the next 10 years and 92 will not have the same (49). The relative risk is still in practice for communicating risk to younger individuals with an elevated level of risk factors; which means as they are young, so their current risk is low, but it is still high compared to a person of same age and sex with ideal risk factors level (48).

2.6 Prediction model and cardiovascular disease

‘In medicine, a prognosis commonly relates to the probability or risk of an individual developing a particular state of health (an outcome) over a specific time, based on his or her clinical and non-clinical profile,’ as defined by Moons K G et al. 2009 (50). Prediction is a common practice in clinical medicine as well as in public health arena and research (66). The physicians use multiple predictors/variables while estimating patients’ prognosis as there remains variation in disease etiology, presentation, and available management options; hence prognostic study requires a multivariable approach to deciding on the important predictors of the outcome of interest in a prediction or risk model (50). As prognosis or risk prediction is characteristically longitudinal in nature; hence a prospective cohort study where subjects are followed-up over time is ideally desirable for optimum measurement of predictors and outcome (66).

The currently available CVD risk prediction models used either logistic, or Cox proportional hazard, or Weibull regression model in identifying appropriate predictors of CVD outcome (9). The predictors which show statistically significant association with the outcome of interest are kept in the multivariable prediction model and by assigning weight to the predictors based on their effect size helps calculating a risk score for every individual; a larger risk scores indicates a higher risk for the outcome (66, 51).

A critical requirement of a risk prediction model is that it predicts satisfactorily in a new but similar population other than those population who has been used to develop the model (116). Usually, the performance of a prediction model in a different population is measured by calibration (how closely the predicted risk approaches the observed risk) and discrimination (how well a prediction model can discriminate those with the outcome from those without the outcome) (9, 47).

In order to facilitate primary prevention a number of risk prediction models, e.g. *Framingham* (54), *SCORE* (16), *QRISK*⁴ 1 (55), *QRISK* 2 (56), *PROCAM*⁵ (57), *Reynolds score* (58), etc. have been developed to identify people at a higher- risk of developing CVD. Framingham and SCORE risk models are the most commonly used among the currently available prediction models (100). Framingham risk prediction score (<https://www.framinghamheartstudy.org>) is the pioneer of risk estimation models so far developed and is based on Framingham Heart Study (Massachusetts, USA), a prospective, single centered, community-based cohort (12). But the generalization of the Framingham risk prediction model to the population of different countries and origins became a matter of concern (13, 14, 15). The difficulties in using Framingham model in local European context led to the development of a new CVD risk scoring system titled SCORE (**S**ystematic **C**oronary **R**isk **E**valuation) for assisting European clinical practitioner (16, 59). The SCORE risk prediction model has been recommended by the Fifth Joint European Task Force on cardiovascular prevention (60).

2.7 The SCORE (Systematic COronary Risk Evaluation) prediction model

The Working Group on Epidemiology and Prevention of the European Society of Cardiology published SCORE risk model in 2003 (16, 59). The objective of the SCORE risk prediction model is to assist the European clinicians by providing better predictive accuracy of an individual's 10-year risk of fatal CVD in the European population (16). The development of SCORE model was considered a larger dataset of 205,178 participants, representing 2.1 million person-years of observation (16). It is a pooled dataset of 12 European prospective studies (Finland, Russia, Norway, UK, Scotland, Denmark, Sweden, Belgium, Germany, Italy, France, and Spain) and has the potential to accommodate more of the heterogeneity in baseline CVD risk

⁴ *QRISK is a CVD risk score based on QResearch database,*

⁵ *PROCAM is a CVD risk score based on PROspective Cardiovascular Munster study*

across European population (16). The majority of the cohort represents the general population though some are occupational, and recruitment of the participants occurred during the 1970s and early 1980s (16). The SCORE project has developed age and sex- specific risk charts based on total cholesterol; systolic blood pressure and smoking status separately for high and low-risk European population (16). The high-risk (cohorts from Denmark, Finland, and Norway) and the low-risk region (cohort from Belgium, Italy, and Spain) were categorized based on examination of CVD death rates standardized for risk factors level in the cohort and also by taking into account the age-standardized national mortality statistics (16).

The SCORE risk prediction tool predicts 10-year risk of CVD mortality (16) which differs from the widely used Framingham risk score which predicts the risk of CVD events (62, 63, 64). SCORE model has chosen cardiovascular mortality as an end point which allows standardization of the endpoint across the different European cohorts and to facilitate recalibration of the function if needed (16, 47, 48). The SCORE model has included stroke (cerebrovascular disease), heart failure and other certain vascular diseases as outcome variable along with coronary heart disease; this is an important feature as same risk factors are responsible for these conditions as well as coronary heart disease and people with a high-risk of cardiovascular mortality are also at risk for non-fatal episodes (48, 61). Framingham risk models have used end points which considered both hard (death) and soft outcome, e.g. coronary insufficiency, an onset of angina, etc. in its different version (62, 63, 64). The CVD risk prediction models also should consider having a clearly defined outcome variable as it helps to prevent coding difficulties, particularly when the function is applied to an external population (9). SCORE prediction model did not consider diabetes as a predictor in the model due to lack of uniformity in the data collection of the SCORE cohorts (16).

2.8 SCORE risk chart interpretation

The SCORE prediction model estimates the probability of 10-year risk of developing fatal CVD events in patients as a percentage (16) and interpretation of this must be done appropriately. If a patient is estimated to have a 10-years CVD risk of 8% - the appropriate interpretation would be to express that if 100 individuals have similar level of risk factors as those of the patient, 8 will experience a CVD event in the next 10 years and 92 will not have the same (49). The SCORE project presents gender specific and color formatted (shade of green, orange, red and dark red) risk chart where based on the level of individual's risk factors (age, systolic blood pressure, total cholesterol, and smoking status), level of risk is expressed as different percentages: < 1%, 1%, 2%, 3%, 4%, 5 - 9%, 10-14% and 15% and over (16). The risk is considered to be low if the SCORE is below 1%, moderate if it is $\geq 1\%$ but less than 5%, high if it is $\geq 5\%$ but less than 10% and very high risk if the score is $\geq 10\%$ (65). Using the SCORE function, the 'third joint force on European guidelines on cardiovascular disease prevention in clinical practice' defined high risk as being having a 5% risk of 10-year CVD mortality in asymptomatic individuals and recommended intensifying preventive interventions beyond that point (11).

2.9 Assessment of performance of a prediction model

The performance of a risk estimation system is done by calibration and discrimination (9, 28, 47). Calibration measures how closely the predicted outcome agrees with the actual observed event (9, 47). Calibration is measured by assessing goodness of fit, where a lower value indicates a better fit, and values below 20 considered as a good fit (47). It can also be done by calculating observed to predicted or expected event ratio (O/P or O/E) where ratio values closer to 1 indicates better fit, values > 1 indicates underestimation, and < 1 indicates overestimation (47). Calibration often assessed visually by dividing the population at risk into quintiles (e.g. deciles)

of predicted risk and plotting the predicted risk versus the observed event rate for each quintile (49). It is also possible by plotting predictions on the x-axis, and the outcome on the y-axis in a graphical assessment where perfect predictions should be on the 45° line and a deviation from this line indicates overestimation or underestimation of the actual number of events (66). The Hosmer-Lemeshow chi-square test is a statistical test for assessing calibration and a P value of <0.05 indicates poor calibration of the model (49, 73, 74).

Discrimination refers to the ability of the function to separate those who will develop the end points from those who will not (9). Discrimination is measured using the area under a receiver operating characteristic curve (AUROC), which is a means for expressing the maximum achievable sensitivity and specificity (28, 47). An AUROC of 1 indicates perfect discrimination, and 0.5 equates to chance, a value of about 0.9 are often achieved for diagnosis test and rarely exceeds 0.8 for a risk estimation (28, 47).

2.10 Performance of SCORE model in different countries

The SCORE risk prediction model has been evaluated in a number of countries which are described below:

Lindman and colleagues evaluated the predictive accuracy of SCORE risk model in Norway by using two population-based surveys (n = 57229) which were linked to the Norwegian Death Registry (17). The number of expected events (E) estimated by the SCORE model was compared with those of observed events (O). The SCORE high-risk model overestimated the CVD deaths in Norway (O/E ratios 0.53, 0.53 and 0.45, for age groups 40–49, 50–59, and 60–69 years in men; and 0.60, 0.45, and 0.37 in women for same age group respectively) (17). However, the SCORE low-risk function predicted reasonably well for men in each age category (O/E ratios

0.85, 0.92 and 0.79), but an overestimation was found for women aged 50–59 and 60–69 years (O/E ratios 0.69 and 0.56, respectively) (17).

Van Dis, I. et al evaluated both the SCORE high and low-risk models and an adapted SCORE-Netherlands (NL) model using a Dutch prospective cohort study (n = 32885) and mortality data from Statistics Netherlands (20). The ratio of the observed-to-expected number of CVD deaths was found to be 0.75 for men and 0.55 for women using SCORE-NL, 0.54 and 0.56 using SCORE-high, and 1.11 and 0.95 using SCORE-low (20). Both the SCORE-NL and SCORE-high overestimated the number of CVD deaths by a factor 1.5–2 in Dutch population level; whereas SCORE-low predicted the number of CVD deaths well (20).

The SCORE high-risk model was found to be strongly correlated in a small Tunisian male cohort (n=164) to the occurrence of cardiovascular death at 10 years ($p < 0.0001$) (67).

The predicted ability of the SCORE high-risk model was evaluated in Central and Eastern Europe and the former Soviet Union, as the high-risk version was recommended by the European Society of Cardiology for this region (22). The World Health Organization MONICA (MONItoring the trends and determinants in CVD, n=15027), the HAPPIEE (Health, Alcohol, and Psychological factors in Eastern Europe, n=20517) studies and the mortality follow-up data from the national and local mortality registers were used for this purpose (22). The high-risk SCORE underestimated the fatal CVD risk in Russian MONICA but performed well (predicted vs observed mortality were close) in most MONICA samples and in Russian HAPPIEE. But it overestimated the risk in the Polish and Czech population (22).

Marques-Vidal P and colleagues used a cross-sectional, population-based study (n = 5773) to compare the predictive accuracy of the original SCORE low-risk model with the calibrated Swiss

version of SCORE functions in estimating 10-year cardiovascular risk in Switzerland (21). The findings suggested that the original SCORE low-risk function adequately predicted CVD death in Swiss population, particularly for individuals aged less than 65 years (21). The calibrated Swiss function provided better risk estimates for older participants over 65 years and classified fewer men and more women in the high-risk category (21).

Vorarlberg Health Monitoring and Promotion Programme (VHM&PP), a large multicentre prospective longitudinal linkage project was used to evaluate the predictive accuracy of the SCORE low-risk model in Austria (19). The predicted risks were compared with the 95% confidence intervals (CI) of the observed events. The SCORE function overestimated CVD mortality in Austrian population (1.5% predicted vs 1.1% observed death in both sexes; which is 2.2% predicted vs 1.8% observed in men and 0.9% predicted vs 0.5% observed in women) (19). Though the SCORE low-risk model over predicted the CVD events yet it was considered as a potential tool in clinical practice in Austria (19).

The SCORE high-risk model was recommended for Germany, but it overestimated the absolute risk by predicting 1.4 times more CVD fatal events than that was predicted by the Framingham model in a study, where the actual number of fatal events was in between the predicted numbers by SCORE high-risk and Framingham models (18). The study suggested the need for recalibration of SCORE high-risk model in German context (18). The recalibrated version of SCORE Germany was developed in 2005 by using a national database and was found to be useful (68). It was evaluated by using two large population-based surveys [SHIP (117) and KORA (118)]. Previously overestimation by the original SCORE high-risk model was reduced considerably by new German model which properly reflected the differences in risk factors and CVD mortality risk among populations within Germany (68).

Scheltens T and colleagues compared the cardiovascular risk predictive ability of the Framingham and SCORE risk models in a Dutch Cohort (n = 39719) where both the models showed good discriminative ability (AUC: 0.86 vs. 0.85), but inadequate calibration (69). The SCORE and the Framingham models showed a Hosmer-Lemeshow chi-square test value of 35 and 64; where a value < 20 is considered appropriate (69).

South Asian population in the United Kingdom showed a higher risk of cardiovascular disease; the predictive performance of FINRISK⁶, Framingham 1991 and SCORE models was evaluated in the South-Asian UK population by Bhopal R et al. using the new Castle Heart Project Population (N=1301) (70). The SCORE model showed rather a lower 10-years risk in all the South Asian groups, but both the Framingham and FINRISK models predicted reasonably well (70).

The Italian national risk charts to assess the probability of developing major fatal and nonfatal cardiovascular events is developed based on the CUORE⁷ project and is recommended by the Italian Ministry of Health for cardiovascular risk assessment (71). The comparison between CUORE and SCORE risk models for low-risk region shows that SCORE model reflected Italian cardiovascular mortality quite well and, correspondingly, Italian cohorts of the CUORE project are quite representative of low-risk European countries cardiovascular mortality (71).

The performances of the Framingham and SCORE risk models in predicting cardiovascular death in France was compared by creating a virtual population based on data representative of the French population and the result was compared with those derived from national vital

⁶ Risk score developed from a large Finish population survey on risk on chronic non-communicable diseases

⁷ The CUORE study is a large prospective cohort follow-up study, including cohorts from the Northwest, Northeast, Centre, and South of Italy.

statistics (72). Framingham overestimated French cardiovascular deaths (predicted over observed ratio: 1.5 in men vs 1.3 in women), but SCORE underestimated the same (predicted over observed ratio: 0.94 in men and 0.85 in women) (72). Framingham showed an exaggeration of coronary deaths among CVD deaths in some cases even exceeded CVD deaths, and the researchers concluded that SCORE should be preferred to Framingham to predict cardiovascular death risk in the French population (72).

SCORE high-risk model was found to overestimate the risk in Germany and Norway (17, 18) which are considered as high-risk countries; whereas SCORE low-risk model over predicted the risk in Austria which was considered as a low-risk country (19)

According to Fourth European Joint Task Force on cardiovascular disease prevention in clinical practice, optimization of risk estimation was suggested by proper country specific recalibration of the SCORE model taking the current national circumstances into account (94). During the late 2000's, country specific recalibration was done in several countries, e.g. Germany, Belgium, Australia, etc. (68, 73, 74). The Belgian researchers developed SCORE Belgium risk model by calibrating SCORE original based on national mortality statistics and risk factor distribution in Belgium (73). Belgian SCORE model was evaluated in a prospective Belgian cohort study; the result indicated good predictive accuracy over the complete range of predicted risk (Hosmer-Lemeshow: $P = 0.14$) of fatal cardiovascular disease over a period of 10 years in Belgium (73).

Similar as the Belgian methodology the AusSCORE model was developed in Australia by recalibrating SCORE original model based on Australian national mortality data and average age-specific and sex-specific levels of CVD risk factor variables from eight Australian large-scale population-based surveys (74). Evaluation of the new chart was done by using 'Blue

Mountains Eye Study, Australia' and was compared with the original SCORE and Framingham models (74). The recalibrated AusSCORE proved to be a valid and reliable method for predicting 10-years CVD risk in the general Australian population (74). It showed good discrimination and calibration capacity (Hosmer–Lemeshow chi-square statistics P value were 0.68 and 0.11 in men and women respectively), much better performance than the original SCORE and Framingham equations (74). In a different study, both high- and low-risk versions of SCORE and Framingham risk models were evaluated in an Australian adult women cohort (n=4487) from National Heart Foundation third Risk Factors Prevalence study by Goh, L. G. H. and colleagues (108). The predicted deaths by the Framingham, SCORE low- and high-risk models were overestimated by 23%, 16% and 75% respectively (108). But the overestimation by the Framingham and SCORE low-risk models were not found significant by the Hosmer-Lemeshow chi-square test, both these models calibrated well and were seen to be suitable for Australian women population for predicting 10-years CVD risk (108).

Similarly, HellenicSCORE was developed to predict 10-year fatal CVD events in Greek population by calibrating the SCORE model based on local mortality and prevalence data from the National Statistical services and ATTICA⁸ epidemiological studies, though evaluation of its predictive ability still awaits a prospective cohort data (59).

⁸ *a population-based health and nutrition study from the Attica province of Greece*

2.11 Canada and the CVD risk assessment tools

There is no cardiovascular risk prediction model available currently for Canadian population which was developed based on Canadian cohort and CVD risk estimation among Canadians is practiced by using CVD statistical models which were developed based on adults who were followed-up in the United States or Europe (29).

The 2009 Canadian Cardiovascular Society (CCS)'s position statement on 'Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease' recommends using the revised Framingham Risk Score (FRS) for estimation of total CVD risk which includes stroke (75) rather than the Anderson KM et al 1991 equation which estimates risk for non-fatal myocardial infarction (MI) and coronary heart disease (CHD) death (62). CVD risk prediction by using FRS is in clinical practice in Canada, and 69% of all Canadian Primary Care Physicians use the FRS model for identifying the risk of their patients for CVDs, compared to the use of other existing risk assessment tools (e.g. PROCAM and Reynold's risk tool (76). Bosomworth et al. 2011 opted for a simpler CVD risk management approach in Canada to make it more attractive to physician and patients (77). Grover A.S et al. validated FRS 1991 model, using the Canadian subjects in the Lipid Research Clinic follow-up cohort study and the calibration was found to be reasonably accurate, but the small number of cardiac events in the cohort provided rather limited scope for validation (29). But to date, there remain no large-scale published studies demonstrating external validation of any of cardiovascular risk assessment tools in the Canadian population. The SCORE risk prediction model was identified as one of the risk assessment models that may be appropriate to use for Canadian population (29). The SCORE Risk model has been extensively studied in European population yet information regarding the use of SCORE risk model in the Canadian context is very limited.

Canada is a multicultural society and consists of heterogeneous population both in terms of ethnicity and lifestyle characteristics (115). Evidence showed that different ethnic groups in Canada have different cardiovascular disease prevalence rates; Canadians of South Asian origin have an increased prevalence of cardiovascular disease compared to Canadians of European and Chinese origin (25, 106) and it is partially explained by an increased prevalence of abdominal obesity, glucose intolerance, hypertriglyceridemia, and low HDL-C amongst the south Asian population (25, 106). The age-standardized cardiovascular mortality significantly varies across different regions in Canada and is noticeable at the province, territory and also at health region level (27). The Canadian Aboriginal people have greater burden of atherosclerosis, higher frequency of CVD than the people of European origin; they also have a higher prevalence of conventional CVD risk factors (26). Manuel DG et al 2003 stated that the death rate from CVD dropped from 702 per 100,000 to 288 per 100,000 men and from 562 per 100,000 to 175 per 100,000 women between 1950 and 1999, though CVD still remains the leading cause of death in Canada (24). This finding indicates a gradual decline in CVD death in Canada. The exact mechanism behind this reduction is not clear, combination of factors like better prevention, treatment and management activities might have played an important role (78).

The cardiovascular disease mortality rate has changed over time in different geographical regions (107). Thus CVD risk prediction model that has been developed based on one region or population or time period will work in a different fashion (e.g. either over or under estimation) when it will be applied to a different region, population, or time other than the original; in such a situation a recalibration process can help overcoming this problem (28).

Given the situation in the absence of a Canadian multivariable risk assessment tool (29), and in the absence of large-scale validation study regarding the performance of other available CVD

risk assessment models in Canadian context it remains unclear whether the recommended CVD risk estimation models can correctly identify the people at risk in Canada. A prospective cohort study is needed to develop a prediction model (66) and a prospective cohort of sufficient size has not been followed in Canada (29). The advantage of SCORE system is that it differs from other functions as it estimates the risk of CVD mortality as opposed to CVD events (which counts both hard and soft events) and recent CVD mortality statistics are easily available in many regions (16).

Canadian Heart Health Surveys Follow-up Study is a longitudinal follow-up of the Canadian Heart Health Surveys (CHHS), which has been linked to the Canadian Mortality Database (CMBD) by Statistics Canada (82, 111). It provides an excellent opportunity to evaluate the performance of SCORE model in the Canadian context. This study will take the opportunity of the presence of CVD mortality and risk factor variable data in Canadian Heart Health Surveys Follow-up Study which will allow an evaluation of how well the SCORE risk prediction model performs to this particular Canadian population.

CHAPTER 3: MATERIALS AND METHOD

This chapter describes the source of data used for this research, which is followed by the description of the variables and the way data analyses was done.

3.1 The data source

The analysis of this study was performed by using the data of Canadian Heart Health Surveys Follow-up study which is a combination of Canadian Heart Health Surveys (CHHS) as baseline study and Follow-up study by linking the CHHS data to Canadian Mortality Database (CMDB).

3.1.1. Canadian Heart Health Surveys (CHHS) is a population based cross-sectional complex survey conducted in ten Canadian provinces - Newfoundland, Prince Edward Island, Nova Scotia, Quebec, Ontario, Saskatchewan, Manitoba, Alberta, New Brunswick, and British Columbia between 1986 and 1992 (79). These surveys at the provincial level were conducted as part of the Canadian Heart Health Initiative and as a collaborative effort among provincial departments of health, Health Canada and The Heart and Stroke Foundation of Canada. The surveys followed a standard protocol – the methods and clinical procedures for all provinces were similar (79). The primary objective of CHHS was to determine the prevalence of Cardiovascular Diseases (CVD) risk factors and participants’ knowledge and awareness of the causes and consequences of these factors at the provincial level (79).

3.1.2 CHHS Study design and participants: Canadian Heart Health Survey used a stratified two-stage probability sampling design to select the study participants. Both male and female aged 18 to 74 years were chosen as study participants in all ten Canadian provinces and the ‘Health Insurance’ registries of each province were used as the sampling frames which contain a

nearly complete listing of the target population as almost all residents are covered by provincial health insurance plans (79).

Two probability weights were calculated by statistical methodologist for each participant within each province to adjust for the unequal probability of selection and non-responses at the home interview (PWGTQ) and clinic visit (PWGTC) (80, 112). The PWGTQ probability weights were used for information collected at home interviews and the PWGTC probability weights were used for information collected during clinic visits. The PWGTC probability weights were used for analyses of the information collected jointly during both home interviews and clinic visits.

3.1.3 CHHS data collection method: Data were collected through 40-60 min long personal interview at home and clinic visit in two stages. At the first stage, the selected persons were visited in their homes to collect the basic demographic data, knowledge of CVD risk factors, attitudes and opinions on heart-related issues. Two blood pressure readings were taken, one at the beginning and one at the end of the interview. At the second stage of data collection, respondents from the first stage came to the clinic to give anthropometric measurements and two additional blood pressure readings usually within two weeks of the home interview. All data were collected by trained nurses (79). Participants who attended both the home and clinic visits were 23,129 from ten Canadian provinces. The response rates were approximately 77% for the home visit and 67% for both the home and clinic visits (80).

3.1.4 Linkage of data: The CHHS Follow-up Study comprises the linkages of CHHS data with the Canadian Mortality Database (CMDB) by Statistics Canada (110, 111). The CMDB record all deaths since 1950 and death events are reported by the provincial and territorial Vital Statistics Registries in Canada. Cause of death information in the CMDB is coded using the

version of the *International Classification of Diseases* (ICD) in effect at the time of death (81). Canada has a national health care system and CMDB covers the entire population, so the chance of missing death events for participants was limited. The data record linkage was performed using computerized probabilistic methods to the Canadian Mortality Database by Statistics Canada. The cause of death was reported by the Statistics Canada according to Intentional Classification of Disease (ICD), 9th (up to December 31, 1999) and 10th (up to December 31, 2004) codes revisions (82). Cardiovascular deaths were identified from the data by the researchers following both ICD-09 and ICD-10 classifications (ICD-9: 390-448; ICD-10: 100-178). If there was no information regarding the death events, participants were considered alive.

The CHHS was a complex survey design, so Statistics Canada calculated the bootstraps weights for the participants based on the PSU (probability sample unit) and strata, which enabled researchers to calculate an accurate value of standard error.

The current study is based on data collected from the three Prairie Provinces (Alberta, Manitoba, and Saskatchewan) for whom bootstrap weights were available and where the linkages of death are done till December 31, 2004. The CHHS data collection in Alberta, Manitoba, and Saskatchewan took place during 1989 to 1990.

3.2 Variables

3.2.1 Outcome variable: The study has considered atherosclerotic cardiovascular mortality as specified by the SCORE project (16) as the outcome variable. SCORE model has defined cardiovascular mortality as per International Classification of Disease version-09 (ICD-9) (83) codes which are enumerated in Table 3.1 on the next page. The corresponding ICD - 10 codes

(84) are also given in Table 3.1, which are adapted from SCORE model evaluation research papers from Australia (74) and Norway (17).

Table 3.1 Definition of outcome as per ICD-09 and ICD-10 classification

	ICD 9 code	ICD 10 code
Hypertensive disease	401 – 405	I10 – I13, I15
Myocardial Infraction	410-414	I20 - I25
Conduction disorders and heart failure:	426 - 429 <i>*Exception: 426.7, 429.0</i>	I44 – I51 <i>*Exception: I45.6, I51.4, & I52</i>
Cerebrovascular disease	430–438 <i>* Exception: 430.0, 432.1, 437.3, 437.4, and 437.5</i>	I60–I69 <i>* Exception: I60, I62, I67.1, I67.5, and I67.7</i>
Disease of arteries, arterioles and capillaries	440 - 443	I70 - I73
Instantaneous death: Death within 24 hrs of hospitalization	798.1, 798.2	R 96.0, and R 96.1

** ICD 9: 426.7 & I45.6 - Anomalous atrioventricular excitation, 429.0 & I51.4 - Unspecified Myocarditis, 430.0 & I60 - Subarachnoid hemorrhage, I52 – Other heart disorders classified elsewhere (bacterial infection, parasitic disease, other infection, rheumatoid carditis etc), 432.1 & I62 - Subdural hemorrhage, 437.3 & I67.1- Cerebral aneurysm non-ruptured, 437.4 & I67.7 - Cerebral arteritis , 437.5 & I67.5 - Moyamoya disease*

3.2.2 Independent variables: The study has considered sex, age, total cholesterol (TC), systolic blood pressure (SBP) and smoking status as independent variables as were used in the SCORE project (16).

Age: The CHHS data (Alberta, Saskatchewan, and Manitoba) has information from people aged 18-74 years. The original SCORE predicting model was developed for the age group of 40 to 64 years old (16). But different age bracket has been used by different countries while validating the predicting ability in their own context {17, 20, 74}. The current research will limit

its analysis among participants aged 40 to 69 years old for analyzing research objectives 2 and 3. For analyzing objective 1, the age limit has been extended within the age bracket of 20 to 74 years.

Sex: The sex of the participants was known from the demographic information of the data set.

Total Cholesterol: The Lipid Research Clinic (LRC) Laboratory, University of Toronto carried out the analysis of the blood samples from all the surveys (113). An 8-hour fasting venous blood sample was obtained using Vacutainer tubes and tourniquet. Strict standard procures were followed while transporting the serum to LRC. The lipid determinations were made according to procedures specified in the LRC Laboratory methods manual, and met strict requirements for standardization (113).

The Total Cholesterol (TChol) level data presented in this study was presented in mmol/L as was given in the database and was categories into three categories – desirable when the TChol level is <5.18 mmol/L, borderline when the TChol level is between 5.18 to 6.19 mmol/L and high when the level is ≥ 6.2 mmol/L (10).

Blood Pressure: Two diastolic and two systolic blood pressure (SBP) readings were obtained during the home interview and another two readings during the clinic visits from each respondent, both at the beginning and at the end of the home interview and at the beginning and end of the clinic visit by the nurses using standard mercury sphygmomanometers. The nurses were trained in the taking of blood pressure measurements according to standardized procedures of the Lipid Research Clinics Program (National Heart and Lung Institute, 1984) (114).

The Systolic blood pressure (SBP) data presented in this database is based on the mean of the four measurements in mm of Hg pressure. The blood pressure was categorised into four categories as per for descriptive purpose – Normal BP (if SBP <120mmHg), Pre hypertensive (if SBP within 120-139 mmHg), Stage I Hypertension (if SBP within 140-159 mmHg) and Stage II Hypertension (if SBP \geq 160mmHg) (114).

Smoking: The information on smoking was recorded as a dichotomous variable – a) **current smokers** include current regular and irregular smokers and b) **current non-smokers** include never and former smokers. The CHHS data lack information on people who quit smoking within the past one year and also information on a number of cigarettes smoked per day.

Individuals with diabetes were not excluded from the study sample in our analysis. The SCORE research group did not exclude people with diabetes diagnosis from the SCORE database used for the development of risk function due to lack of uniformity on diabetes data among the SCORE study cohorts (16).

The variables those were used in this research and their names in the data set are given in the following Table 3.2.

Table 3.2 List of Variables in the study and the name of variables in the dataset

Name of the variables used in analysis	Name of variables in the CHHS
probability weight for questionnaire	pwgtq
probability weight for clinic/blood	pwgtc
Age in years	age
Age category	New_Age_Category
Sex	sex

Total Cholesterol (mmol/L)	tchol
Cholesterol category	tchol_cat
Current smoker	cursmoke
Diabetes Mellitus – Yes/No	diabet
High density lipoprotein (mmol/L)	hdl
Systolic blood pressure (average) in mm Hg	msys
Systolic blood pressure category	msys_cat
Currently on hypertensive treatment (yes/No)	bprxnow
Time to event (till Dec 2000) in year	NT_event_yr
High absolute risk - Male	highMale_CVDRISK
High-risk percentage category- Male	High_RiskMale_Per_Category
Low absolute risk - Male	LowM_CVDRISK
Low-risk percentage category- Male	LowMale_RISKPERCENT_Category
High absolute risk - Female	highf_CVDRISK
High-risk percentage category - Female	HighFe_RiskPercent_cat
Low absolute risk - Female	Lowf_CVDRISK
Low-risk percentage category - Female	LowFemal_RiskPercent_cat
Previous heart attack	everha
Previous stroke	everstr
Previous other heart disease	othhd
Dependent variables	
All Cardiovascular mortality till 2004	CVD_all_mortality
SCORE defined CVD death till 2004	NCVD_all_mortality
SCORE defined Coronary death till 2004	CHD_all_mortality

SCORE defined Non-coronary CVD death till 2004	NCHD_all_mortality
SCORE CVD death till December 2000	death10
SCORE Coronary death till December 2000	CHD_death10
SCORE Non-coronary CVD death till December 2000	NCHD_death10

3.3 Selection of Samples and exclusion criteria

Participants were excluded if they have had a history of CVD event at baseline – heart attack, stroke, and any other heart disease. Any missing data related to total cholesterol, systolic blood pressure and smoking was also excluded. The selection of a sample from the CHHS data was presented in the following Table 3.3. The unweighted number of the participants is presented here but later while presenting the research findings weighted (either PWGTQ or PWGTC as required) number will be presented. A total of 7148 (unweighted value) men and women in the age group of 20-74 years from Manitoba, Saskatchewan, and Alberta participated in CHHS Follow-up Study. From this, a total of 2800 (unweighted value) men and women within 40-69 years age group were selected for the analysis. Participants with the previous history of heart attack (n=153), stroke (n=104) or any other heart disease (n=334) were further excluded. Participants (n=388) with incomplete data on total cholesterol, systolic blood pressure, and smoking, were also excluded. Finally, a total sample of 1965 (unweighted) men and women remained for the analysis. It is to be noted that some participants have more than one reason for exclusion. Thus the total number of the sample size (40-69 years) is not the result of direct subtraction of the exclusion criteria from the total survey participants (18-74 years).

Table 3.3 Flow diagram of the selection of the study sample from participants (Manitoba, Saskatchewan and Alberta) in Canadian Heart Health Survey (CHHS)

Participants	Male	Female	Total	
18-74 years	3501	3647	7148	
40-74 years	1728	1735	3463	
40-69 years	1386	1414	2800	
History of previous Cardiovascular event				
	Previous heart attack	108	45	153
Not Included	Previous stroke	66	38	104
	Previous other heart disease	152	182	334
Not Included	Incomplete data on total cholesterol, systolic blood pressure, smoking,	161	227	388
Cardiovascular risk prediction group (40-69 years)		983	982	1965

* Some participants have more than one reason for exclusion, so sample size (40-69 years) number does not represent direct subtraction of exclusion criteria from the total survey participants (18-74 years)

** This study sample (40-69 years) is taken for analysing objective 2 and objective 3.

3.4 Statistical Analysis

CHHS is a complex survey design, so as per the CHHS guidelines the study will report all the results as weighted values. The CHHS database present two weights - weight based on the question (PWGTQ) and based on clinical data (PWGTC) (80, 112). Data was analysed by using statistical package SPSS 23.1 and Microsoft Excel 2010. For objective 01, questionnaire weight (PWGTQ) was used and for objectives 02 and 03, clinical weight (PWGTC) were used. Descriptive statistics were based on a weighted analysis in order to produce nationally representative and unbiased estimates. Analysis plan of each objective is described in the following section.

3.4.1 Analysis of objective 01: to calculate the Standardized all-cause and cardiovascular mortality of the CHHS Follow-up Study population

For analysis of Objective 01, we have considered CHHS participants of 20 to 74 years of age. Probability weight PWGTQ was considered for analyzing objective 01, as all participants (20-74 years) who participated in the survey interview were included in this analysis. Age was divided into 6 categories (20-29, 30-39, 40-49, 50-59, 60-69 and 70-74 years). Follow-up of death was considered till December 2004.

Determination of Cause of Death: The analysis was conducted for death due to ‘all-causes’ and ‘cardiovascular diseases’. In CHHS Follow-up Study, the cause of death was reported by the Statistics Canada according to International Classification of Disease (ICD), 9th (up to December 31, 1999) and 10th (up to December 31, 2004) codes revisions (82). Cardiovascular events were identified during previous data analysis by the researchers (ICD-9: 390-448; ICD-10: I00-I78) (82, 111). If there was no information regarding the death events, participants were considered alive (82). The total number of ‘all-cause death’ and ‘cardiovascular death’ at each of the above mentioned age-categories was calculated through cross-tabulation by using statistics package SPSS 23.1. CHHS recommended weight PGWTQ was used during analysis.

Calculation of person-year: Each member of the Canadian Heart Health Survey (CHHS) cohort accumulated person-time from the date of entry (*September 1989 - July 1990*) until the earliest of the following: the date of death for deceased, or the ending date of the study which is the time (*December 01, 2004*) till which statistics Canada has linked the mortality data with CHHS. For each cohort member, person-year at risk by age group, sex, and the province of residence were

calculated from the date of registration mentioned above till the day of death or the end date of the study.

Calculation of standardized mortality: Sex-specific age-standardized mortality was calculated for all-causes of death (total mortality) and death due to cardiovascular disease. Cardiovascular mortality was standardized as our main analysis (objectives 02 and 03) is focused on cardiovascular death. Canadian population of 1991 was considered as a Standard population which is extracted from Statistics Canada CANSIM Table 051-0001 (85).

Participants were categorized by sex and 10-year age group with an exception of 70-74 years group which was a 5-year age group (20-29, 30-39, 40-49, 50-59, 60-69 and 70-74 years). Direct standardization method was used for standardizing the mortality in CHHS data which has given the death rate that would be expected in 1991 Canadian population of 20-74 years old if it had experienced the same age-specific event rate as in the CHHS population. Following formula of direct standardization was used for calculation (105):

$$\text{Age-standardized Death Rate} = \sum_{i=1} (W_i P_i) * 1000,$$

where P_i is the age-specific crude death rate for each of the above mentioned age group of the CHHS population; W_i (or the weight) represents the stratum-specific proportion of population in the standard population (1991 Canadian population). It can also be shown as the following formula:

Age-standardized Death Rate = total expected death /total standard population * 1000, where, the number of the total expected deaths is the summation of age specific expected events in each age-stratum. Age categorized expected event is calculated by applying the age specific death rate of the study population to the age distribution of the chosen standard population.

By using the above mentioned calculation sex-specific age standardized death rate for all-cause mortality and CVD mortality were calculated for each province (Alberta, Saskatchewan, and Manitoba) separately (presented in annex section) and for all province together (presented in result section).

For all-cause mortality, we compared the age standardized death rate of CHHS population with the crude death rate of Canadian 1991 population; which was extracted from Statistics Canada CANSIM Table 102-0504 (86). For cardiovascular disease mortality, death due to major cardiovascular diseases (I00-I78) was extracted from Statistics Canada CANSIM Table 102-0551 for the year 2000 (87) and the corresponding population was extracted from CANSIM Table 051-0001 0001 (85). Statistics Canada website does not provide a report on age categorised major CVD (I00-I78) death both at national and at the provincial level before the year 2000. As such we calculated the crude CVD death rate of Canada for the year 2000 and standardized that (both age and sex) with the standard population of 1991. Similarly, CVD death reported in CHHS Follow-up Study was also age and sex-standardized with Canadian 1991 population. The major cardiovascular death in CANSIM table from Statistics Canada is defined as death from 'I00-I78' as per ICD-10 classification (87).

3.5.2 Analysis of objective 02: To estimate the 10-year risk of having fatal cardiovascular event in CHHS population by using both the SCORE high- and low-risk models

For analysis of Objective 02, CHHS participants of 40 to 69 years of age were considered. Probability weight PWGTC was considered for analyzing objective 02, as all participants (40-69 years) who participated in the survey interview and clinic visit were included in this analysis. Age was categorised into three categories: 40-49, 50-59 and 60-69 years.

First, the cumulative 10-year incidence of fatal Cardiovascular death (observed CVD death as defined by SCORE model) in the CHHS sample was calculated and was stratified as per defined age categories. To ensure a 10-year follow-up any fatal cardiovascular events occurred after December 2000 was excluded as CHHS data collection in Alberta, Saskatchewan, and Manitoba took place during 1989 to 1990.

The calculation of expected 10-year risk estimation for fatal cardiovascular events was based on baseline survival coefficients for Coronary Heart Disease (CHD) and Non-Coronary CVD separately for men and women from SCORE high- and low-risk regions. The total effect of smoking, serum total cholesterol, and systolic blood pressure was calculated by applying the beta coefficients of the SCORE equations. The expected number of atherosclerotic cardiovascular death was calculated by using both the SCORE high and low-risk models on the individually measured systolic blood pressure, total cholesterol and smoking status of all respondents of the CHHS participants. SCORE equations are sex specific (16). Both the equations provided with absolute risk at an individual level and finally, the expected number of cardiovascular death was calculated as sum of individual absolute risks. In SCORE equation, the survival was estimated

using Weibull model that consisted of two components – (i) baseline or underlying survival probabilities and, (ii) function describing the effect of risk factors on the baseline risk (16). Separate baseline risk functions were calculated for male and female. Two different types risk charts were presented by the SCORE researchers; one based on total cholesterol and the other on total cholesterol /HDL cholesterol ratio (16). This thesis has taken into consideration the risk-chart based on total cholesterol.

Following steps were followed to estimate the 10-year risk of fatal cardiovascular disease by SCORE research group (16) and accordingly syntax (SPSS 23.1) were developed for the current research which is provided in Appendix 1 and 2.

Step 1

Calculate the underlying risks for coronary heart disease and for non-coronary cardiovascular disease separately for the person's age now and for their age in ten years' time, using the values for alpha and p shown in Table A (page 38). The underlying survival probability, S_0 is given by:

$$S_0(\text{age}) = \exp\{ - (\exp(\alpha))(\text{age} - 20)^p \}$$

$$S_0(\text{age}+10) = \exp\{ - (\exp(\alpha))(\text{age} - 10)^p \} \quad (1)$$

Step 2

Using the coefficients in Table B (page 38), calculate the weighted sum, \mathbf{w} , of the risk factors cholesterol, smoking and systolic blood pressure. Two weighted sums will have to be calculated, one for coronary heart disease and one for non-coronary cardiovascular disease.

Smoking is coded as 1 for a current and 0 for a non-smoker, so no value for smoking has to be entered if the person is a non-smoker. Cholesterol is measured in mmol/L and SBP is measured in mmHg. The weighting for each risk factor is denoted by beta.

$$W = \beta_{\text{chol}}(\text{cholesterol} - 6) + \beta_{\text{SBP}}(\text{SBP} - 120) + \beta_{\text{smoker}}(\text{current}) \quad (2)$$

Step 3

Combine the underlying risks for coronary heart disease and for non-coronary cardiovascular disease, at the person's age and at their age ten years from now (four calculations) which were calculated in step 1 with the weighted sum of a person's risk factors from step 2 for the two end-points, coronary heart disease and non-coronary cardiovascular disease to get the probability of survival at each age for each cause.

$$S(\text{age}) = \{S_0(\text{age})\}^{\exp(w)}$$

$$S(\text{age}+10) = \{S_0(\text{age}+10)\}^{\exp(w)} \quad (3)$$

Step 4

For each cause, calculate the 10-year survival probability based on the survival probability for the person's current age and their age in 10 years' time:

$$S_{10}(\text{age}) = S(\text{age}+10) / S(\text{age}) \quad (4)$$

Step 5

$$\text{Calculate the 10 year risk for each end-point as } \mathbf{Risk}_{10} = 1 - S_{10}(\text{age}) \quad (5)$$

Step 6

Combine the risks for coronary heart disease and non-coronary cardiovascular disease by adding them: $\mathbf{CVDRisk}_{10}(\text{age}) = [\text{CHDRisk}(\text{age})] + [\text{Non-CHDRisk}(\text{age})]$ (6)

The following Table A provides regions specific (high- and low-risk) coefficient tables for CHD and Non-CHD CVD deaths for men and women which were adopted from original SCORE publication (16). Table B provides information on coefficients for individual risk factor on CHD and Non-CHD CVD which is also adopted from Conroy R et al 2003.

Table A Coefficients for Eq. (1)						Table B Coefficients for Eq. (2)		
		CHD		Non-CHD CVD				
		α	p	α	p	CHD		Non-CHD CVD
Low-risk	Men	-22.1	4.71	-26.7	5.64	Current smoker	0.71	0.63
	Women	-29.8	6.36	-31.0	6.62	Cholesterol (mmol/L)	0.24	0.02
High-risk	Men	-21.0	4.62	-25.7	5.47	Systolic BP (mmHg)	0.018	0.022
	Women	-28.7	6.23	-30.0	6.42			

Tables A and B adopted from Conroy R et al 2003

3.5.3 Analysis of objective 03: To assess how closely the predicted risk of having cardiovascular death approaches the actual death observed in CHHS population

Calibration measures how closely the predicted risk approaches the observed risk (9, 47). More specifically, it is the agreement between the probability of developing the outcome of interest within a certain time-period as estimated by the prediction model and the observed outcome frequencies (9, 47). A widely used method for this analysis is to calculate the Hosmer-Lemeshow (HL) chi-square test by comparing an observed and an expected number of events in each risk category as defined by risk deciles (49, 73, 74). As CHHS Follow-up Study followed a complex survey design and HL chi-square test is not a suitable test for complex survey design. We followed the following methods to find how closely the predicted risk approached the observed risk:

- (i) After calculating the absolute risk in objective 02, the predicted risk was categorized as per sex and the age group specified before (40-49 years, 50-59 years and 60-69 years). The observed number of CVD death is also categorized as per sex and age group. Then the predicted risks were compared with the estimated 95% confidence interval of the observed events in each age category and sex group.

- (ii) The risk ratio of the observed to expected events (O/E) and their 95% confidence interval was also calculated as per age and sex category where a risk ratio of 1 indicates a perfect calibration.
- (iii) The observed number of fatal CVD events (O) in the CHHS cohort and the expected number of CVD deaths (E) both by SCORE high and low equation were plotted by categories of absolute risk as per SCORE high and SCORE low function, and then the ratio of O/E number of fatal CVD was calculated for the different risk functions (17, 20).

CHAPTER 04: RESULTS

Results of the data analysis are presented in this chapter. The findings are presented in two sections as follows: (1) description of the samples which includes demography and the study variables, and (2) results of the research question as per each research objective

4.1 Description of the study population

Descriptive analysis is restricted to the cohort that was selected for analyzing objectives 02 and 03. After applying the inclusion and exclusion criteria as mentioned in the method section, a total of 1965 participants (unweighted number) were finally selected for analyzing objective 02 and objective 03. The participants are from three provinces of western Canada – Alberta, Saskatchewan, and Manitoba. The Canadian Heart Health Survey data collection for these three provinces took place during 1989 and 1990. The follow-up period was kept till December 2000 to have a 10-year risk assessment. The baseline characteristics of the study sample are highlighted in Table 4.1.

Table 4.1 Summary of baseline risk factors in the CHHS study by sex and age group

	Male			
	40-49 years	50-59 years	60-69 years	All (40-69 years)
% of N	45.8%	31.4%	22.9%	49.4%
Age in years, mean (\pm SD)	44 (2.6)	54.9 (3)	64.6 (2.8)	52.2 (8.7)
SBP (mmHg), mean (\pm SD)	123.4 (11.5)	131.3 (16.4)	134 (17.3)	128.3 (15.3)
SBP \Rightarrow 140mmHg, (%)	8.6%	25.2%	34.1%	19.7%
TC (mmol/L), mean (\pm SD)	5.28 (0.9)	5.56 (0.9)	5.50 (0.9)	5.4 (0.9)
Hypercholesterolemia, \Rightarrow 6.2mmol/L, (%)	16.7%	20.7%	22.5%	19.3%
Current smoker (%)	32.7%	21.7%	31.5%	29%
Diabetes (%)	3.5%	8%	6.5%	5.6%

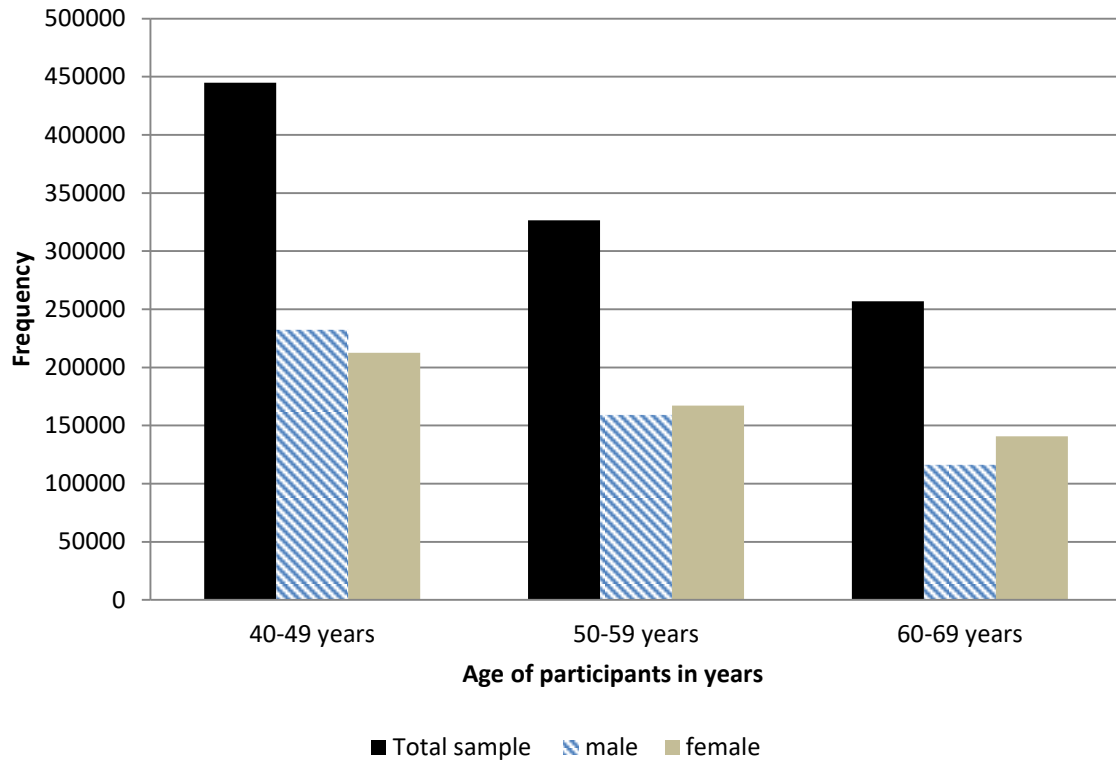
Female				
	40-49 years	50-59 years	60-69 years	All (40-69 years)
% of N	40.8%	32.1%	27%	50.6%
Age, mean (\pm (SD)	44.5 (2.9)	54.7 (2.9)	64.5 (2.9)	53.2 (8.6)
SBP (mmHg), mean (\pm SD)	116.8 (13.5)	126.2 (15.7)	136.2 (17.8)	125.1 (17.4)
BP \Rightarrow 140mmHg, (%)	6.45%	21.18%	36.76%	19.38%
TC (mmol/L), mean (\pm SD)	4.99 (0.78)	5.46 (0.95)	5.9 (1.06)	5.4 (0.99)
Hypercholesteremia \Rightarrow 6.2mmol/L, (%)	5.3%	20.1%	40.1%	19.5%
Current smoker (%)	23.9%	22.5%	20.4%	22.5%
Diabetes (%)	4.5%	4.3%	8.1%	5.4%

** Results are expressed as weighted value of mean \pm standard deviation or as weighted percentages (%). SBP: Systolic Blood Pressure, TC: Total Cholesterol.*

4.1.1 Gender and age structure

The study population (40-69 years) consists of slightly higher proportion of females (50.4%) than males (49.6%). The mean (SD) age at baseline was 52.7 (\pm 8.7) years; the mean age of female (53.2 \pm 8.6) was a bit higher than that of male (52.2 \pm 8.7). The population was divided into three equal age strata (40-49, 50-59 ad 60-69 years) and the younger sub group found to be higher proportion in both men and women (male: 46% and female: 41%) than other two sub-groups. Participants of strata 60-69 years represent lowest proportions (male; 23% and female: 27%) than other two sub-groups. Figure 4.1 shows the distribution of age in both male and female.

Figure 4.1 Gender specific age distributions in the CHHS study sample



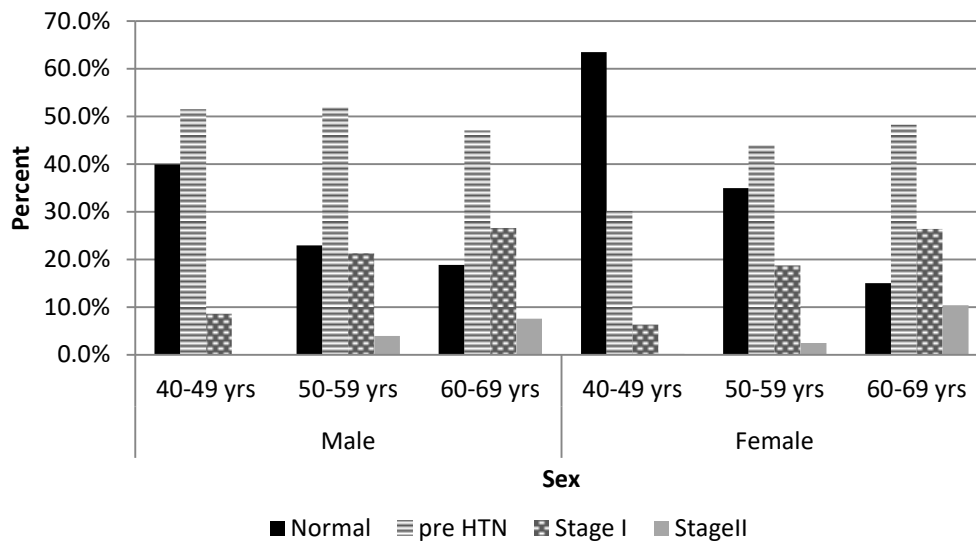
* Results are expressed in weighted value

4.1.2 Distribution of risk factors

The baseline risk factors distribution of the study participants is enumerated in Table 4.1. The mean (SD) systolic pressure in male (128 ± 15 mmHg) participants was slightly higher than females (125 ± 17 mmHg). A similar trend was observed in all three age categories. A higher proportion of females (41%) was found to be in normal blood pressure category than males (30%); on the contrary more males (50.6%) were found in the pre-hypertension stage than females (39.4%). Though almost equal proportion of both sexes was found to be hypertensive (19.7 vs 19.4); yet higher proportion of females (10.4%) in age category 60-69 years was found to be stage II hypertensive (Systolic blood pressure \Rightarrow 160 mmHg) than males (7.6%) of the similar age group, opposite was observed in the age strata 50-59 years (2.5% vs 3.9%). The mean

total cholesterol level was found to be almost similar in both sexes (M: 5.42 ± 0.94 vs F: 5.4 ± 0.99); the mean level of total cholesterol increases with the increasing age categories which was observed in both sexes. Forty percent of women of 60-69 years old has TC level of ≥ 6.2 mmol/L which is almost half (22.5%) in men of similar age group; interestingly a higher proportion of men (16.7%) in younger age group (40-49 years) has high cholesterol level than their female counter parts (5.3%). Twenty-nine percent (29%) of the male and 22.5% of female participants are found to be current smoker in the study cohort. Female participants in younger age group (40-49 years) show slightly a higher proportion of current smoking (23.9%) than that of their older group (22.5% for 50-59 years and 20.4% for 60-69 years age group). Among male participants, the younger (40-49 years) and older groups (60-69 years) have a higher proportion of current smoking (32.7% and 31.5% respectively) than that of the middle age group (50-59 years) which is 21.7%. Figure 4.2 shows the distribution of different categories of Systolic blood pressure in the male and female population of this study.

Figure 4.2 Distribution of systolic blood pressure by age and sex group in the study sample



* Results are expressed in weighted value

4.2 Result of objective 01: to calculate the standardized all-cause and cardiovascular mortality of the CHHS study population (Alberta, Saskatchewan and Manitoba)

A total of 6866 un-weighted participants of 20-74 years old who entered the CHHS cohort were analysed for objective 01 of the study. Female ($n: 3514$) represents 50.2% of the participants. The study population are from Manitoba ($n=2661$), Saskatchewan ($n=2066$), and Alberta ($n=2139$). The population in different age categories of 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years and 70-74 years represents 26%, 27% 18%, 14%, 11% and 4% (weighted %) of the total participants in the study. The follow-up time was calculated in person year which is presented in Table 4.2. The participants contributed an average of 14.4 person-years/ subject of follow-up. During the follow-up period till December 2004, a total of 936 all-cause deaths (*female: 376, male: 560*) occurred in all three provinces. Of the total reported deaths, 340 were from the disease of the cardiovascular system (*Female: 129, Male: 211*) which represents 33.42% of all-cause mortality (*Female: 27.72% and Male: 37.65%*).

Table 4.2 Age specific breakdown of the person year contributed (weighted), all-cause and cardiovascular deaths (weighted) in CHHS population

Age in years	Person year (PY)		All-cause deaths		Cardiovascular deaths	
	Male PY	Female PY	Male	Female	Male	Female
20 - 29 years	5629977	5575591	4125	3347	590	233
30 - 39 years	5995787	5973053	9329	1344	2912	0
40-49 years	3945686	3686871	15595	13590	6387	1993
50 – 59 years	2867394	3025928	24999	17816	6331	2926
60 – 69 years	1895186	2433391	58804	47407	23962	15180
70 – 74 years	632443	762435	30097	22549	13645	9067
Total	20966473	21457268	142949	106053	53827	29399

The crude mortality rate for all-cause mortality was found to be 5.87 per 1000 person years for both-sex. Male reported to have a crude mortality of 6.82 per 1000 person years compared to 4.94 per 1000 person years in the case of females. The province specific (Alberta, Saskatchewan, and Manitoba) sex categorised standardized mortality rate has been given in the appendix section (Appendix 04 and 05).

The 1991 Canadian population in the age category of 20-74 years was used as the standard population, where female represents 50.2% of the population (85). The population in different age categories (20-29, 30-39, 40-49, 50-59, 60-69 and 70-74 years) represents 24%, 26%, 20%, 14%, 12% and 4% of the total participants within 20-74 years segment of 1991 Canadian population (85). A total of 90192 all-cause mortality was reported to occur in Canada in 1991 for the population within age group of 20-74 years; male: 56690 and female: 33502. The all-cause mortality rate of the standard population was found to be 5.99 per thousand male population and 3.50 per thousand female populations as shown in Table 4.3a.

The standardized mortality rate for CHHS population (20-74 years) of both sexes by taking the 1991 Canadian population as the standard population was found to be 6.74 per 1000 population which is 7.95 in male and 5.62 for per 1000 female population respectively which has been enumerated in Table 4.3b.

The CHHS Follow-up Study reported a total of 211 major CVD deaths (unweighted number) in male and 129 (unweighted number) of those in female which gives crude mortality rate (weighted) of 2.57 per 1000 person-years (PY) in male and 1.37 CVD deaths (weighted) per 1000 PY in female in the CHHS population (Table 4.4b). A total of 23171 major cardiovascular deaths (female: 7393) were reported in the year 2000 in Canada which gives a crude major CVD

mortality rate of 1.10 deaths per 1000 population for both sex; in male it is 1.50 and in female: 0.69 per 1000 population respectively in Canada (Table 4.4a).

Table 4.3a All-cause mortality rate (20-74 years): Canada 1991 population

Age in years	Canada 1991 population: male		Canada 1991 population: female	
	Population: male	Death rate /1000 population	Population: female	Death rate/1000 population
20-29	2334307	1.18	2259724	0.41
30-39	2476196	1.43	2456766	0.66
40-49	1913946	2.69	1891296	1.58
50-59	1291758	7.34	1286602	4.21
60-69	1078284	20.06	1199050	10.67
70-74	364432	38.81	470193	20.75
Total	9458923	5.99	9563631	3.50

Table 4.3b Standardized all-cause mortality rate (20-74 years): CHHS population

Age in years	CHHS population: male		CHHS population: female	
	Death rate/ 1000 X PY*	Expected death	Death rate/ 1000 X PY*	Expected death
20-29	0.73	1710	0.60	1357
30-39	1.56	3853	0.23	553
40-49	3.95	7565	3.69	6971
50-59	8.72	11262	5.89	7575
60-69	31.03	33457	19.48	23360
70-74	47.59	17343	29.57	13906
Total	6.82	75190	4.94	53722

Standardized all-cause mortality rate for CHHS male:

$$(75190/9458923*1000) = \mathbf{7.95/1000 \text{ population}}$$

Standardized all-cause mortality rate for CHHS female:

$$(53722/9563631*1000) = \mathbf{5.62/1000 \text{ population}}$$

* PY = Person Years

The CVD death rates in both the CHHS population and the Canada 2000 population were standardized by using 1991 population of Canada as standard. The standardized rate for major CVD death of Canadian 2000 population was found to be 1.39 per 1000 male and 0.67 per thousand female populations. The standardized mortality rate of major CVD death was found to be 2.31 per 1000 population for both sex; 3.05 and 1.61 per 1000 male and female population respectively in CHHS population. The sex and age categorised standardized mortality rate from the major cardiovascular disease for the age group 20-74 years old of 2000 Canada population and CHHS population have been shown in Table 4.4a and Table 4.4b.

Table 4.4a Standardized CVD mortality rate (20-74 years): Canada 2000 population

Canada 2000 CVD mortality: male				Canada 2000 CVD Mortality: female		
Age in years	* Standard population: male	Death rate/ 1000 population	Expected death	* Standard population: female	Death rate/ 1000 population	Expected death
20-29	2334307	0.04	91	2259724	0.023	51
30-39	2476196	0.12	295	2456766	0.054	133
40-49	1913946	0.50	948	1891296	0.169	319
50-59	1291758	1.64	2125	1286602	0.556	716
60-69	1078284	5.15	5555	1199050	2.132	2556
70-74	364432	11.22	4089	470193	5.645	2654
Total	9458923	1.50	13103	9563631	0.69	6429

Standardized CVD mortality rate for Canada 2000 male: $(13103/9458923)*1000 = \mathbf{1.39/1000 \text{ Population}}$

Standardized CVD mortality rate for Canada 2000 female: $(6429/9563631*1000) =$

0.67/1000 population

* Canada 1991 population

Table 4.4b Standardized CVD mortality rate (20-74 years): CHHS population

CHHS CVD mortality: male				CHHS CVD mortality: female		
Age in years	* Standard population	Death rate /1000 X PY	Expected CVD death	* Standard population	Death rate /1000 X PY	Expected CVD death
20-29	2334307	0.10	245	2259724	0.04	94
30-39	2476196	0.49	1203	2456766	0.00	0
40-49	1913946	1.62	3098	1891296	0.54	1022
50-59	1291758	2.21	2852	1286602	0.97	1244
60-69	1078284	12.64	13633	1199050	6.24	7480
70-74	364432	21.58	7863	470193	11.89	5592
Total	9458923	2.57	28894	9563631	1.37	15432

Standardized CVD mortality rate for CHHS male: $(28894/9458923)*1000 = 3.05/1000$ population

Standardized CVD mortality rate for CHHS female: $(15432/9563631)*1000 = 1.61/1000$ population

* Canada 1991 population

4.3 Result of objective 02: To estimate the 10-year risk of having fatal cardiovascular event in CHHS population by using both the SCORE high- and low-risk models

During the 10-year of follow-up period, 6.74% of the study population (40-69 years) experienced all-cause mortality in the validation sample. A total of 7.86% of male compared to 5.65% of female were registered dead during the reported period in our study sample. 1.9% of male and 0.9% of female registered to have CVD death as per definition of the SCORE project. Death due to CVD constitutes almost one-quarter of total male death (24.2%) and 16% of female all-cause death. CVD deaths were found to be two-fold higher in male than in female. Death due to coronary heart diseases alone constitutes about 61.4% of CVD deaths in male and 72.3% of that in female respectively. The age and sex categorized observed CVD deaths in the study population have been enumerated in the following Table 4.5.

Table 4.5 Observed CVD and CHD* deaths (weighted) in the study population (40-69 years)

Age categories	Male		Female	
	CVD death	CHD Death	CVD death	CHD death
40-49 years	1447	1447	252	252
50-59 years	2239	1958	1021	305
60-69 years	5986	2537	3366	2836
Total	9672	5942	4639	3393

*CHD: Coronary Heart Diseases.

By using the SCORE high-risk model, a total of 2.98% of the study population expected to experience CVD deaths while SCORE low- risk estimated that 1.73% of the study population will experience the same with in next 10 years. The expected or predicted number of fatal CVD events that were estimated by both the SCORE high and low-risk models and the observed number of fatal events in both sexes at each age category level are shown in Figure 4.3a and 3b.

Figure 4.3a Observed and predicted number of fatal events in the CHHS male population

a. Male

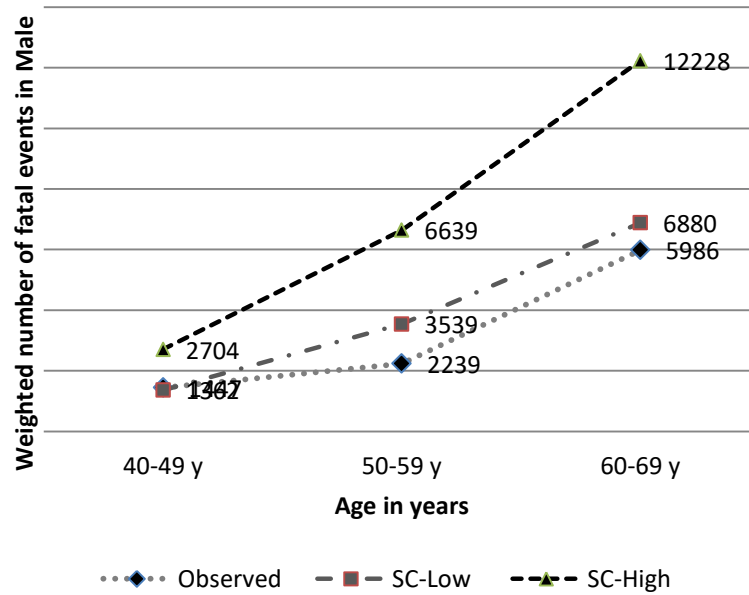
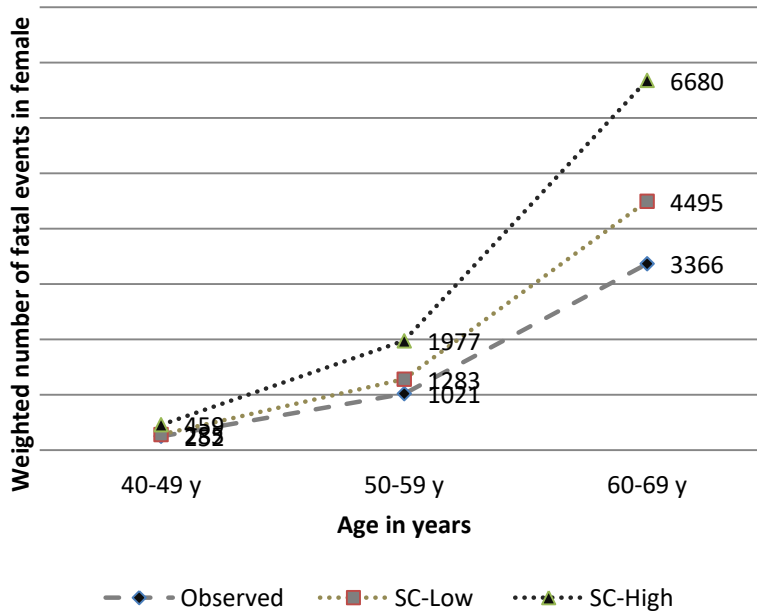


Figure 4.3b Observed and predicted number of fatal events in the CHHS female population

b. Female

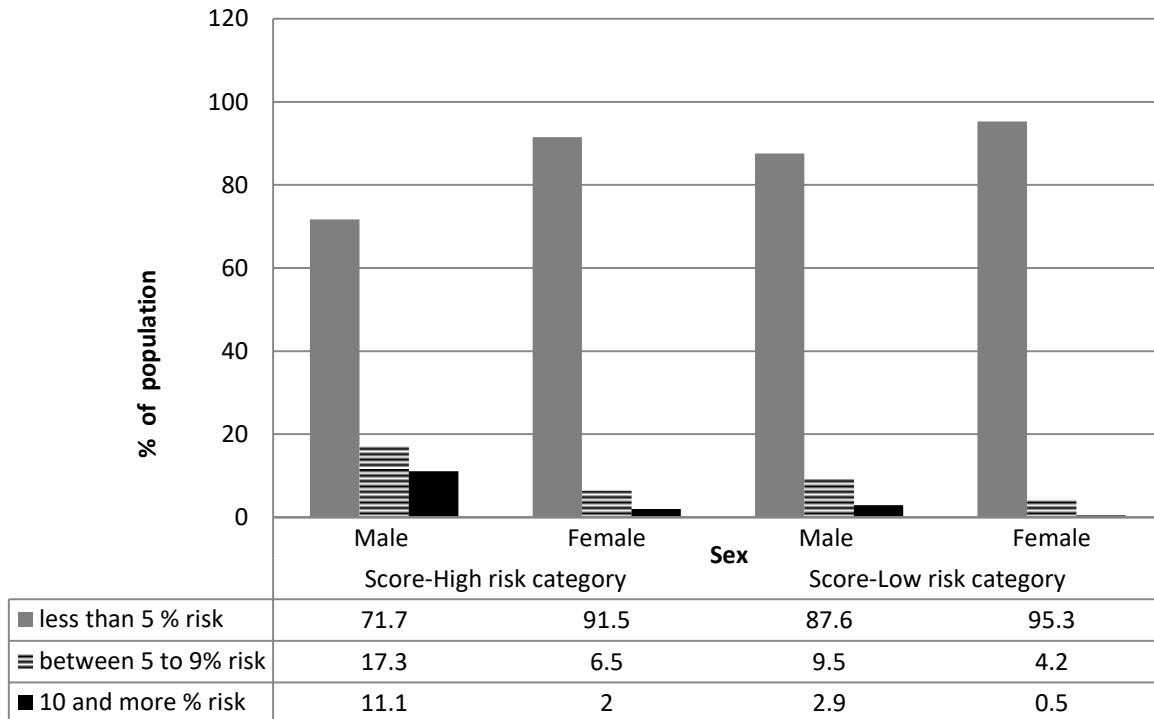


Number of fatal cardiovascular events (weighted) within 10 years of the Canadian Heart Health Survey population and the estimated events in the same population with the SCORE high- and low-risk models (SC-High, SC-Low).

The numbers of observed and predicted events were found to be increased as the age increases in both male and female (Figures 4.3a and 4.3b). A total of 2704, 6639 and 12228 fatal CVD events were predicted in male for age categories 40-49, 50-59 and 60-69 years old by SCORE high-risk model. SCORE low-risk model predicted fatal events were 1362, 3539 and 6880 respectively in the same age categories in male. The SCORE high-risk model predicted 459, 1977 and 6680 fatal CVD events for age categories 40-49, 50-59 and 60-69 years of female and for same age categories female, the events were 285, 1283 and 4495 as predicted by the SCORE low-risk model.

Based on Score high- and low- risk model categories, the percentages of persons who did not have CVD at baseline, 12.4% (Score-low) and 28.4% (Score-high) of men were estimated to have an increased CVD risk, defined as having a 10-year risk of CVD mortality of 5% and above. In women, these are 4.7% and 8.5% respectively (Figure 4.4).

Fig. 4.4 Distribution of 10-year cardiovascular mortality risk in CHHS population

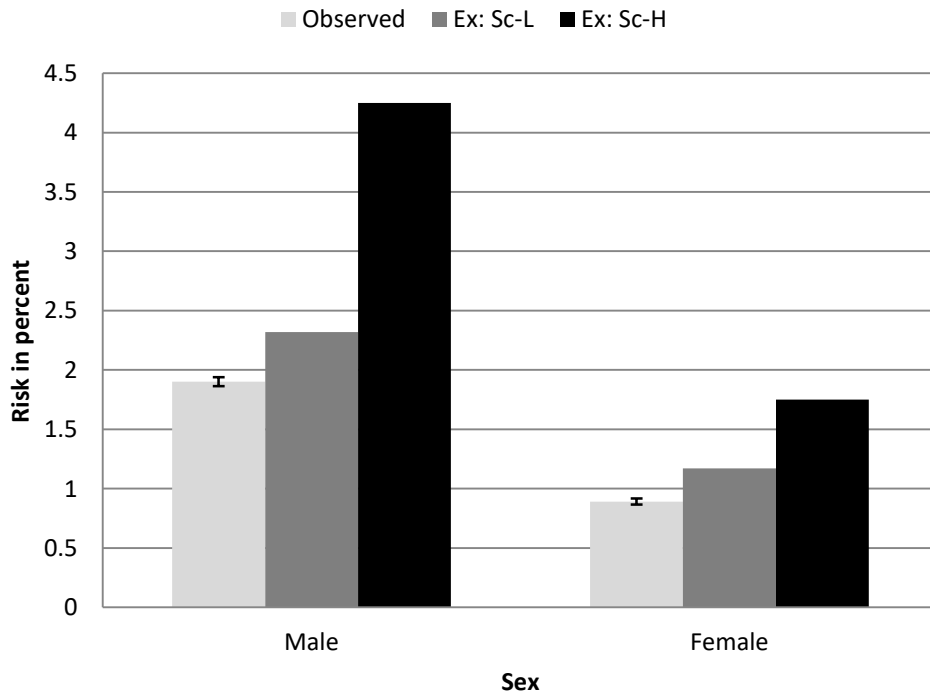


As per both the Score high- and low-risk models, almost 100% of male of 40-49 years are having a 10-year fatal CVD risk of below 5 percent. A quarter (24%) of men within 50-59 years age category possess a 10-year CVD risk of $\geq 5\%$ as estimates by the Score high-risk model but the percentage drops to 5% for SCORE low-risk model. Similar for age group 60-69 years are 89.2 and 47.3 percent respectively. Interestingly almost 100 percentage of female participants in the age group 40-49 and 50-59 years fall below 5 percent of the risk for both the SCORE models. Risk increases with age in female and one third (31.2%) of the female within age range 60-69 shows 10-year CVD risk of 5 percent and above in SCORE high-risk category and 17.2 percent in SCORE low-risk category.

4.4 Result of objective 03: To assess the calibration of SCORE equation by comparing the expected and observed number of cardiovascular death.

Figure 4.5 illustrates the fatal cardiovascular events predicted by the SCORE low and high-risk model compared with the estimated 95% confidence interval of the actual observed events.

Figure 4.5 Ten-year risk of fatal Cardiovascular events: observed versus predicted



Ex: Sc-L and Ex: Sc-H indicate expected death by SCORE low- and high-risk model

Over a period of 10-year, the observed absolute risk of cardiovascular death in CHHS population was found to be 1.9% (95% CI: 1.87, 1.92) in male and 0.9% (95% CI: 0.87, 0.90) in female. This was compared with 2.32% (2.28, 2.36) in male and 1.17% (1.14, 1.19) in female as estimated predicted risk by applying SCORE low-risk equation. The predicted absolute risk by applying Score High-risk equation was found to be 4.25% (4.19, 4.30) in men and 1.75% (1.72, 1.79) in women.

To analyze how closely the observed fatal CVD events match with the expected events which were estimated by SCORE high and low-risk model, we calculated the O/E (observed/expected) ratio where a value of 1.0 indicates a perfect agreement. The age and sex stratified ratio of observed and expected number of events are presented in Table 4.6.

Table 4.6 The ratio of observed over expected CVD deaths: CHHS population

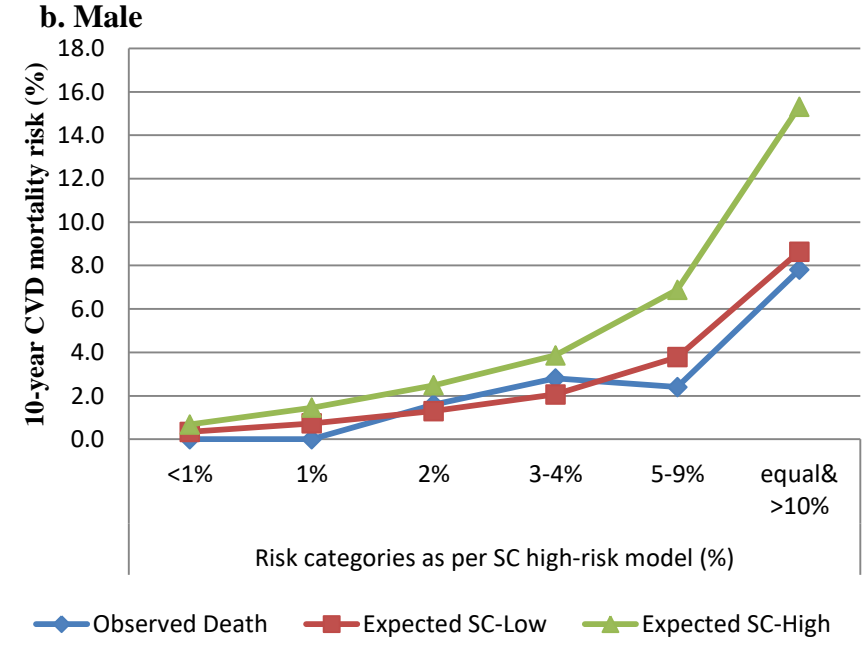
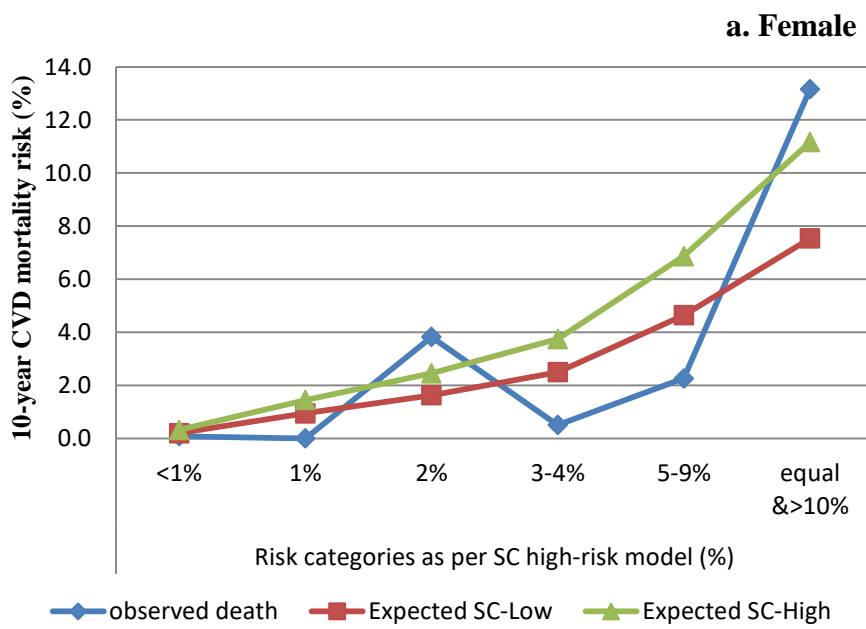
Sex	Age in years	Ratio O/E _{SCORE-high} (95% CI)	Ratio O/E _{SCORE-low} (95% CI)
Male	40-49	0.54 (0.50, 0.57)	1.06 (0.99, 1.14)
	50-59	0.34 (0.32, 0.35)	0.63 (0.60, 0.67)
	60-69	0.49 (0.47, 0.50)	0.87 (0.84, 0.90)
Female	40-49	0.55 (0.47, 0.64)	0.88 (0.75, 1.05)
	50-59	0.52 (0.48, 0.56)	0.80 (0.73, 0.86)
	60-69	0.50 (0.48, 0.53)	0.75 (0.72, 0.78)
Total Male	40-69	0.45 (0.44, 0.46)	0.82 (0.80, 0.84)
Total Female	40-69	0.51 (0.49, 0.53)	0.77 (0.74, 0.79)

The low-risk model shows a better agreement between the observed and expected number of deaths in all age categories of female participants (0.88, 0.80 and 0.75 respectively) than those estimated by the high-risk model in female (0.55, 0.52, 0.50 respectively). The high-risk model estimated almost double the number of fatal events in each age category of female. Similarly, the low-risk model also shows good agreement in 40-49 and 60-69 age categories of male participants (1.06 and 0.87 respectively). Overall male shows better agreement between an observed and expected number of deaths (0.82 vs 0.77) than female when using the low-risk SCORE model. The high-risk model shows overestimation through all age categories of male (0.54, 0.34, 0.49 respectively) as of female. Though the female participants' show fairly a similar

overestimation trend through all age categories but in the case of male the overestimation varies by age categories and it's more pronounced at age category 50-59 years where the predicted death was found to be almost 3 times more than observed death. The overestimation of death by high-risk model at the eldest age group (60-69 years) for both male and female are almost similar {(0.49 (95% CI - 0.47, 0.50) and 0.50 (95% CI - 0.48, 0.53 respectively)}.

Figure 4.6 presents plotted representation of the observed and predicted absolute 10-year CVD mortality risk (%) both in male and female as per risk categories of SCORE high-risk model. The observed risk of CVD fatal events compared well with the predicted risk by SCORE-low model (O/E ratio: 0.82 in male and 0.77 in female) but risk is almost half that of predicted by SCORE-high model in female (O/E-SC high: 0.51) and a further less in men (O/E-SC high: 0.45) as shown in Table 4.6. This trend is present almost in all age categories of male and female (Table 4.6) but it is not that well marked in all risk categories (as per SCORE high-risk) in female (Figure 4.6) but shows consistent overestimation in male (Figure 4.6). In female observed absolute risk is found to be more than the estimated risk by the high-risk model in the population having a risk of 2% (1.5 times with SCORE-high) and in the population having risk more than 10% (Figure 4.6). Similarly, Figure 4.7 also presents plotted representation of the observed and predicted absolute 10-year CVD mortality risk (%) both in male and female as per risk categories of SCORE low-risk model. The overestimation of absolute risk by SCORE high-risk model and somewhat better agreement of risk by SCORE low-risk model is marked in all age risk categories of both sex except in female at risk of equal and more than 10%, where the observed risk is much higher than the both models (4 times than SCORE-low and almost 3 times more than SCORE-high model).

Figure. 4.6 Observed and expected absolute 10-year risk of CVD mortality using the SCORE high-risk model: CHHS participants



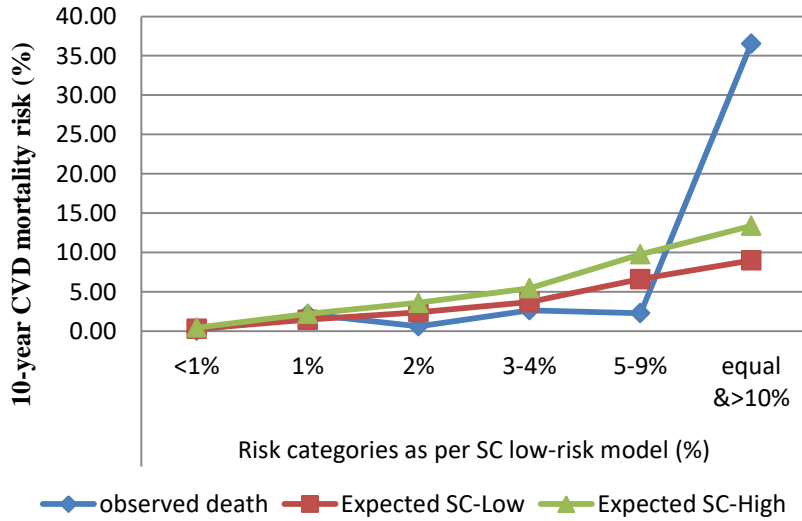
57

Risk %	<1	1	2	3-4	5-9	>10
# at risk	293618	80677	40027	58682	33588	13680
O/E SC-Low	0.43	0.00	2.35	0.20	0.49	1.75
O/E SC-High	0.27	0.00	1.56	0.14	0.33	1.18

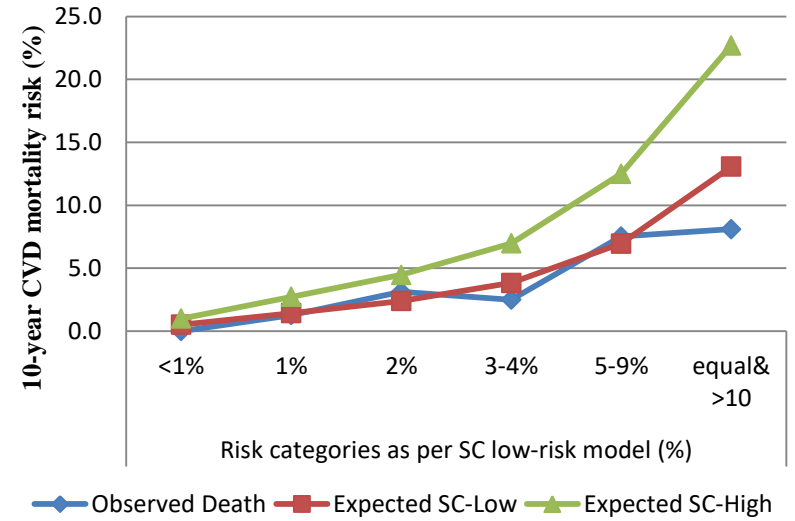
Risk %	<1	1	2	3	5-9	>10
# at risk	122672	99330	60939	81062	87720	56290
O/E SC-Low	0	0	1.20	1.37	0.62	0.90
O/E SC-High	0	0	0.63	0.73	0.34	0.51

Figure. 4.7 Observed and expected absolute 10-year risk of CVD mortality using the SCORE low-risk Model: CHHS participants

a. Female



b. Male



85

Risk %	<1	1	2	3-4	5-9	>10
# at risk	345973	71309	48829	28702	21906	3554
O/E SC-Low	0.25	1.48	0.25	0.72	0.35	4.06
O/E SC-High	0.16	0.98	0.17	0.48	0.23	2.73

Risk %	<1	1	2	3-4	5-9	>10
# at risk	219571	96441	64371	64685	48307	14638
O/E SC-Low	0	0.89	1.31	0.65	1.08	0.62
O/E SC-High	0	0.47	0.70	0.36	0.60	0.36

CHAPTER 05 DISCUSSION

The purpose of this study was to evaluate the predictive performance of SCORE cardiovascular risk prediction model in Canada by using the Canadian Heart Health Survey Follow-up Study data. More specifically this research has compared the expected number of atherosclerotic cardiovascular deaths predicted by both the SCORE high- and low-risk models from CHHS Follow-up Study with the observed number of CVD deaths registered in the same.

This chapter begins with the discussion of the main findings as per the research objectives and then tried to relate these to evidence those existed in this field. This chapter also focuses on the strength and limitation of the study and tries to make a conclusion from the findings. Direction for future research has also been outlined in this chapter.

5.1 Discussion on objective 01

In objective 01, Canadian 1991 population of 20-74 years old was taken as the standard population (85) to standardize the ‘all-cause’ and ‘cardiovascular’ mortality (20-74 years) registered in CHHS Follow-up Study dataset.

The analysis has demonstrated marked differences in both the ‘all-cause’ and ‘cardiovascular’ mortality rates between CHHS Follow-up Study population and those of Statistics Canada 1991 population. It showed an excess of ‘all-cause’ and ‘cardiovascular’ mortality rates in CHHS study population. Higher all-cause mortality is present in all age categories except 20-29 years group in male and 30-39 years age group in the female. If Canadian 1991 male population of 20-74 years old had similar age-specific death rates as of CHHS Follow-up study population, then it would have got a mortality rate of 7.95/1000 male which is almost 1.33 times more than the

death rate of the standard male population of the same age which is 5.99/1000 male population (86). Similarly, the standardized all-cause mortality for female (5.62/1000 female pop) was found to be 1.6 times more than that of 1991 Canadian female all-cause death, which is 3.50/1000 female population (86). As CHHS is a complex survey, hence the weighted proportion of the population in each age category was found to be almost similar as that of the 1991 Canadian population of the same. The study further standardized the registered all-cause deaths in CHHS data set with 1991 Canadian population from Manitoba, Saskatchewan, and Alberta (85); as current study data was collected from those three provinces. The results were found to be similar as of before; standardized death rate for male was found to be 7.75, and for female it was 5.39 per thousand respective populations.

Canadian socioeconomic database from Statistics Canada website, the CANSIM (Canadian Socio-economic information management system) provides age and sex categorized information on cardiovascular death for all Canada together from the year 2000 onward; no province-wise, age-classified CVD mortality data is available before the year 2000 (31, 87, 88). Differences between major CVD (I00-I78) mortality rates as registered in CHHS data and as reported in CANSIM table for the year 2000 in Canada (88) were observed in this study. The crude death rate from major CVD (I00-I78) for the age group 20-74 years was found to be 1.50/1000 male and 0.69/1000 female population in the year 2000 in Canada (88), which when standardized with Canadian 1991 population became 1.39/1000 male and 0.67/1000 female respectively. The CHHS Follow-up Study presents a standardized (by Canadian 1991 population) major CVD mortality rate (for the age group 20-74 years) of 3.05/ 1000 population in male and 1.61/1000 in the female, which is higher than the major CVD mortality rate reported by Statistics Canada in 2000 for all age group (0 to 99+years) in male (2.68/1000 male) and almost similar to female

(1.64/1000 female population) (88). As per the Heart and Stroke Foundation Canada report, the standardized all CVD mortality rate (as per ICD-9 - 390-459 & ICD10: I00-I99) for all age group (+90 years) was found to be 3.06, 3.07 and 3.27 per 1000 male population in Alberta, Saskatchewan, and Manitoba respectively during the year 1995-99 (89). The same for the female was 1.91, 1.78 and 1.96/1000 population in the mentioned provinces respectively during the same period (89). The current study population for objective 01 has considered age group of 20-74 years and major CVD (ICD 10: I00-I78 & ICD-9: 390-448) mortality rate, unlike the Heart and Stroke Foundation report (89). Thus no comparison is made with the Heart and Stroke Foundation report, but an idea has been tried to give about the CVD mortality rate found in the CHHS follow-up study dataset. The major CVD mortality rate (standardized with 1991 population) in CHHS Follow-up Study was found to be 3.45, 2.85 and 2.41 per thousand male and 1.39, 2.01 and 1.62 per thousand female population in Alberta, Saskatchewan, and Manitoba respectively (see Appendix 03).

Based on the findings, it's hard to explain the reason behind this over represented 'all-cause' and major 'cardiovascular' mortality in The CHHS Follow-up study dataset. In the following paragraph, the CHHS Follow-up Study process is given in brief (adopted from the NET⁹ proposal) which might put some light on this issue.

The Canadian Heart Health Surveys were conducted in 10 provinces from 1986 to 1992; a second survey was conducted in Nova Scotia in 1995. Later, the Canadian Heart Health Surveys Follow-up Study, a five-year New Emerging Team (NET) project was initiated in 2004 with a purpose to study the impact of individual- and community-level factors on the relationships between obesity, other chronic disease risk factors, and mortality. The cross-sectional CHHS

⁹ *Canadian Heart Health Survey was termed as New Emerging Team (NET) project*

data had the potential to be served as a baseline for a longitudinal data linkages exercise to explore the influence of chronic disease risk factors on mortality. Initially, A. Edwards CHHS Database Centre, Memorial University linked the CHHS dataset with 1991 census data. Later, the dataset was sent to Statistics Canada for linking it to the Canadian Mortality Database by using a probabilistic method. Finally, the final data was stripped of personal information to make an ‘anonymized longitudinal database containing ecological-level and mortality outcome data’ and send back to the research team from Statistics Canada. Linkages rules involved comparison of text string matches (e.g. surname=surname), or number matches (e.g. birth year differ by less than 2 years) and the outcome of this comparison was defined, e.g. full agreement, partial agreement, missing or disagreement (110). We assume a ‘very slim’ possibility of duplication of the count in case of full agreement and partial agreement. We also have to be cautious while comparing these two death rates as two different definitions (incidence density in CHHS population and cumulative incidence in standard population) were used for the calculation. The CHHS Follow-up Study project was closed in 2010. No resource is currently available to check the linkage information. This data has been used already for research exploring the association between metabolic syndrome and cardiovascular deaths (82). Thus, a decision was made to proceed with the analysis using the registered number of deaths in the dataset. However, we will be referring the findings to the CHHS Follow-up Study data and will be cautious while extrapolating to the Canadian context.

5.2 Discussion on objectives 2 and 3

To the best of my knowledge, this is the first-ever attempt to evaluate the European developed SCORE CVD risk prediction model performance in a large Canadian cohort comprises of both men and women. In the present study, the observed and a predicted number of CVD deaths

among 40 to 69 years old men and women with no history of CVD at baseline in the CHHS Follow-up Study cohort was compared.

There remains a dearth of published information regarding the performance of SCORE prediction tool in North Americans Context. Two separate SCORE risk models are available for high- and low-CVD risk regions in Europe respectively (16). The European cohorts which were used to develop SCORE model were categorised as high- and low-risk population by the SCORE researchers based on CVD death rate standardised for risk factor levels in study cohort and also by taking into account the age-standardised death rates in their national mortality statistics (16). Both risk versions of SCORE prediction model were used for this research given the situation no North-American cohort participated in developing the SCORE risk model.

The findings of this study show that the deaths that were predicted by the SCORE high-risk model was overestimated by a factor of 2.2 in male and 1.9 in female than the observed number of deaths in the CHHS cohort during a follow-up of 10 years. SCORE low-risk version performed better in predicting yet it predicted more than the observed deaths by a factor of 1.2 in male and 1.3 in the female. The overestimation found to be increased with age in women as predicted by SCORE low-risk model but the high-risk model didn't show any age-specific pattern rather showed similar overestimation across all age group. In male, the overestimation was unaffected by age as predicted by both the high and low-risk versions of SCORE model.

As discussed under objective one, that the all-cause and CVD mortality in our data set are reported to be more than the national level. In such a situation we may assume that the ratio of deaths predicted by original SCORE model to that of observed deaths at national level would be even more if the mortality reported in our data were similar as that of the national level.

Twelve European cohorts were used to develop the SCORE risk prediction model to provide a European scoring system (16). The cumulative CVD death rate by the age of 65 years varied widely among the participating countries – in men it ranged from 2.81% in Spain to 12.8% in Finland and in women it was from 0.94% (Spain) to 2.66% (Finland) in the same countries (16).

As per the definition of the SCORE project, a cumulative CVD death rate by the age of 69 years was found to be 1.9% and 0.9% in the male and female population respectively in the CHHS Follow-up study data. The cumulative CVD death rate by the age of 65 years (not shown in the result section) was also analyzed to have an idea about the position of CHHS cohort in comparison with those of other SCORE participating countries. Cumulative CVD death rates by the age of 65 years were found to be 1.1% in male and 0.8% in female in CHHS Follow-up study. These findings are even lower than the cumulative CVD death rate of Spain (male- 2.81% and female- 0.94%) who has the lowest rate amongst the participating cohorts of the SCORE project (16). The CHD death (coronary heart disease death) as a percentage of CVD death was found to be 82.4% in male and 80.02% in female in CHHS data. These are at the higher end in male and in female when compared with the SCORE cohorts; where the highest value (84%) observed in Finish men and 70% in Italian female (16).

Recruitment of participants in SCORE participating European cohorts took place during the seventies and eighties (16) before the widespread introduction of preventive measures and treatment protocols of CVD management. The CHHS data collection (Alberta, Saskatchewan, and Manitoba) took place during 1989 to 1990 which explains the much lower rate of CVD death in our data set. However, DG Manuel et al. 2003 found that between 1950 and 1999 the CVD death rates in Canada dropped from 702 per 100,000 to 288 per 100,000 men, and from 562 per 100,000 to 175 per 100,000 women (24). Statistics Canada also reports a gradual decline in

mortality rate from major cardiovascular disease; for men, the age-standardized mortality rate fell from 268.3 per 100,000 male in 2000 to 159.1 in 2012, and for women, these figures are from 164 to 96.9 per 100,000 female (88). The twenty countries with the lowest CVD mortality rates (during mid to the late 1990s) as reported to the World Health Organization; the Canadian men ranked 4th (after Japan, France, and Spain) and the women ranked 3rd (after Japan & France) to have lowest CVD mortality rates (89). Eight of twelve SCORE participating countries were among these twenty countries reported here (89). This probably classifies Canada to be a low-risk country for CVD mortality.

The level of risk factors in different cohorts which were used developing the original SCORE model varied widely – as for example, current smokers in men varied from 68% in France to 39% in Germany; in women, it was 47% in Denmark to 12% in Spain (16). Mean systolic blood pressure in men varied from 145 mmHg in the UK (BRHS) to 129 mmHg in Denmark and in women, it was found to be 140 mmHg in Finland to 120 mmHg in Spain. (16).

The mean and percentages of risk factor levels in CHHS Follow-up study participants (40-69 years) were found to be lower than the SCORE participating cohorts - e.g. systolic blood pressure: Male - 128mmHg, Female – 125mmHg, total cholesterol: Male - 5.4 mmol, Female - 5.4 mmol, and smoking: Male - 29%, Female - 22%. The mean risk factor levels of CHHS study participants of 40-65 years (similar age categories of SCORE cohort) were also found to be at lower level - e.g. systolic blood pressure: Male -127 mmHg, Female – 124 mmHg, total cholesterol: Male - 5.4mmol, Female - 5.3 mmol, and smoking: Male - 29%, Female - 24%. Lower cumulative CVD rates and lower mean risk factor levels (baseline risk) in our data indicate that it belong to a low-risk region and which explains the overestimation of CVD death by SCORE high-risk model.

Interestingly the SCORE high-risk model overestimated the number of CVD deaths in a Norwegian study participant taken between 1985-'92 though Norway was considered as a high-risk region (17). Study participants from 'Norwegian Counties Study' recruited between the year 1974-'78 were amongst the cohorts used for developing the SCORE risk chart (16). Similarly, the SCORE high-risk model overestimated CVD risk in a German and Dutch population respectively; though both were considered to belong in high-risk regions (18, 20). Austria is considered as a low-risk country; however the low-risk model overestimated the risk in Austria (19); whereas the low-risk model performed well in Dutch, Iceland and Norwegian cohorts but these countries were considered to be in the high-risk region (17, 20, 90). Stenlund H and colleagues thought the decrease in CVD incidence and mortality in Sweden since 1970 probably had altered the baseline hazard on which Swedish SCORE chart is based and this may be one of the possible explanations for overestimation of CVD death by the same model using cohort from 1990-'94 (91).

Hense and colleagues discussed broadly that the risk estimation based on cohort studies that started 20-30 years ago are likely to overestimate risk in current condition (92, 93). Similarly, Graham and Cooney stated 'one size does not fit all when estimating the risk of cardiovascular death' in an editorial (109) while discussing on the study paper by Vikireva et al on evaluating SCORE in Central and Eastern Europe and Former Soviet Union (22). Cooney and colleagues also stated that 'changing CVD mortality in different geographical regions over time' leads to different behavior of a risk prediction model in a population, or region or time period other than the original one based on which it was developed (28). The current study result also shows that risk function derived from European population of around a decade ago tends to overestimate CVD risk in the Canadian population of the nineties when they were at a much lower risk.

During this declining CVD mortality era, the fourth Joint European Task Force on cardiovascular disease prevention in clinical practice suggested optimizing risk estimation by recalibrating the SCORE risk charts to local conditions to allow for time trends in both mortality and risk factor distribution (94). Many European countries have developed their own SCORE risk estimation chart by taking local baseline risk and mortality into consideration (21, 59, 68, 73, 90).

Though the cardiovascular mortality in Canada has reduced significantly over the period of time (24, 88, 89), but there remains no clear-cut answer or single reason behind this reduction. There is evidence that overall improvement in CVD management which include improved in prevention activities, better diagnosis, care, and treatment, positive lifestyles change etc. factors might have played an important role in this reduction of CVD mortality (78). Changes in coronary care and secondary prevention were found to be strongly linked with declining coronary endpoints in WHO MONICA population as found by Tunstall-Pedoe H and colleagues (95). During the period 1980 through 2000, the decrease in the U.S. coronary heart disease deaths was almost equally credited to improve in evidence-based medical therapies and reductions in major risk factors (96). Similarly, the decrease in Coronary heart disease mortality rates in Ontario (1994-2005) was found to be associated primarily with trends in improving risk factors and improvements in medical treatments, each explaining about half of the decrease (97). The increase in diagnosis and treatment of hypertensive patients has led to decreased mortality and hospitalization due to CVD in Canada. (98).

The SCORE high-risk model (16) identified that about 3 out of ten men and 1 in 10 women in our study population were at high-risk (equal & > 5% risk) of having fatal CVD within next ten years. The SCORE low-risk model (16) identified 1 in 10 men and 1 in 20 women to be at risk of the same. Nine out of 10 men and 3 out of 10 women within age range 60-69 years identified to

have a risk of 5% and above by the SCORE high-risk model (16) which is about 5 and 2 in 10 men and that of women respectively identified at risk by low-risk model (16). Both the high- and low-risk models showed limited value of its application in younger people, particularly in women as nearly cent percent of them at and below 59 years old were identified having 10-year CVD mortality risk less than 5%. Similarly, cent percent of male within 40 years age bracket are identified as having risk below 5% by both the risk models. The limited application of absolute risk in younger people is also mentioned elsewhere (28, 47, 74). Increasing age is a strong risk factor for CVD and it acts as an exposure time to other risk factors hence younger people even with high-risk factor will be at lower absolute risk level which might conceal a high absolute risk (28). The Fourth European Joint Task Force team has suggested using relative risk method in identifying young people having low absolute risk but the higher relative risk (94).

Multivariable risk assessment tools have mainly developed and studied in white population in developed countries (100). SCORE risk model was developed from a large pool of European data set (twelve cohorts from different European countries) with the intention to capture the regional variation in CVD risk as Framingham risk score performed not so well in Europe (16). The participating European countries are the predominantly white ethnic origin. The validation and recalibration of SCORE model have also been done mostly in European countries (17, 18, 19, 20, 21, 22, 68). Thus it is not known whether SCORE baseline absolute risk is similar to that in other population of different ethnic origin. Canada is a multicultural and multiethnic society - 20.6% of total population (Census 2011) represents foreign born and Asia (including the Middle East) was Canada's largest source of immigrants during the past five years (99). The cardiovascular morbidity and mortality observed to be varied across people from different ethnicity in Canada; South Asian-born and Chinese-born Canadians has identified different

mortality rates from cardiovascular diseases compared to individuals born in Canada (25). Similarly, aboriginal people in Canada are also found to be at a higher risk of having CVD compared with their European counterparts (26). The CVD risk estimation by Framingham risk score (FRS) was suggested to adjust depending on the racial and ethnic background (53) and a recalibrated version is developed in England for using in south Asian, black, Chinese and Irish people. (100). However, SCORE risk level varied between ethnic groups when absolute risk was estimated amongst immigrant and Norwegian population (101) and SCORE high-risk model accurately estimated CVD risk in Malaysian male but underestimated the same in female (102). The SCORE model gave unexpected low 10- year CVD risk in south Asians compared with white Europeans when applied to Newcastle Heart Project data in the United Kingdom, whereas the FINRISK and Framingham models resulted in higher estimated risk among south Asians (70).

Our data does not have information on ethnicity hence we did not analyse the relationship between ethnicity and CVD mortality. Canada is a multi-ethnic society where the baseline risk of CVD varies among the different population; baseline risk is a major factor in the predictive ability of the CVD risk model. Thus exploring the predictive ability of the SCORE model among the people of different ethnic origin in Canada would be interesting and will generate new knowledge.

5.3 Strength and limitations

The first strength of this study is that this research has added new knowledge to cardiovascular research field in Canada as it is the first ever study in Canada where SCORE CVD risk model is evaluated using local data. The second strength of this study is the use of the Canadian Heart Health Survey (CHHS) data which has a large sample size that represents the Canadian

population. The third strength of this study is the linkages of Canadian Mortality Database (CMDB) with CHHS by Statistics Canada to form a cost-effective new prospective cohort. CHHS linked with CMDB has allowed exploring the relationship between the traditional CVD risk factors and CVD mortality in a cost-effective way. A prospective cohort study is required to follow-up for sufficient duration of time to have ‘time to event’ analysis, which is costly and time-consuming.

However, the study has some limitations which need to be addressed. In the absence of a prospective cohort data regarding CVD risk factors and mortality in Canada, this linked dataset was used for analysis. Although the CHHS is a widely used dataset which has a large sample size and represents the Canadian population, yet the standardized all-cause and CVD mortality which are registered in our dataset (CHHS linked data with CMDB) were found to be not in agreement with the national rate. There were not enough sources available to verify this finding and previous researchers have already used this dataset to find the relationship between risk factors and CVD mortality (82). Thus, the analysis was decided to carry out. The result might not reflect real Canadian context, yet it added valuable knowledge to Canadian CVD research arena.

Hosmer-Lemeshow (HL) chi-square test is a widely used method for assessing the calibration (49) (how closely the prediction has meet the observed value of a prediction model). But HL chi-square test is not a suitable method for determining calibration when using complex survey dataset (CHHS Follow-up Study is a complex survey); we have used observed over Expected or predicted (O/E) ratio method for assessing calibration where a value of 1 indicated a perfect calibration (22).

Discrimination refers to the ability of the risk prediction model to separate those who will develop the end point from those who will not and the ‘area under a receiver operating characteristic curve (AUROC)’ is a well-used method for measuring it (28). The current research did not perform ROC analysis for assessing the discriminative capacity of the SCORE risk model due to the limited capability of the available software. CHHS Follow-up study is a complex survey, and proper weight was used for its analysis. SPSS does not provide the option for analyzing ROC for complex survey data that needs to be weighted by survey-weight. STATA Corporation was communicated in this regard and found that currently, none of STATA’s command that calculate the area under a ROC curve and the confidence interval can accept sampling weights (email attached in the appendix).

One of the major limitations of SCORE equation is lack of family history in the prediction model, which has shown to be strongly associated with the increased risk of CVD (119, 120).

5.4 Conclusion

The cardiovascular disease is one of the leading causes of death in Canada. Both in the clinical and public health practices, it is recommended to identify people at a higher risk of having fatal CVD event by using the risk prediction model and bringing them under prevention and treatment package. Canada does not have its CVD risk model and relies on models developed in different populations. The gradual decline in CVD mortality prevalence and shifting composition of population are playing an important role in determining CVD epidemiology in Canada. Given the situation, this study evaluated the predictive performance of the European SCORE CVD risk prediction model for the first time in Canada by using the CHHS Follow-up Study population. SCORE is a widely researched CVD risk assessment tool in Europe that required local level

adjustments for its use. This study revealed that both the high- and low-risk SCORE models overestimated the CVD mortality in both men and women of CHHS cohort; although the low-risk version performed better than the high-risk version. The finding of this study echoes the performance of the SCORE model in other countries; the drawback of using 'prediction models' obtained from one population, region or period to a different scenario other than the original one. Thus this study suggests the need for recalibration of the SCORE model by taking into account of the local Canadian CVD risk situation before implementing in clinical practice. SCORE is a widely used simple risk model which was developed based on a few risk variables and by taking CVD mortality as outcome. Adoption of such a simpler model after proper recalibration will further enrich CVD management practice in the Canadian adult population.

5.5 Future research

This study has provided valuable information regarding the performance of the SCORE CVD risk prediction model in a Canadian dataset. The results are similar as observed in other low-risk settings where the predicted risk of having CVD was overestimated by this model. CHHS Follow-up dataset showed higher CVD death rate than the National value, yet the cumulative CVD death rates (till the age 65 years) in the study population was lower than those of the participating cohorts in the original SCORE study. It is suggested to have further research where the Canadian National CVD death rate will be reflected.

This study could not perform ROC (Receiver Operating Characteristic Curve) analysis to find the discriminative ability of the SCORE model as the linked dataset represents a complex survey design. Similarly, the Hosmer-Lemeshow (HL) chi-square test (49, 73, 74) was also could not be used for measuring the calibration. So we suggest further exploring the performance of SCORE model in the Canadian context by using the national mortality data along with age and sex-

specific distribution of the major CVD risk factors from any Canadian population-based surveys (if possible pooling all possible surveys in Canada) which will allow performing a proper calibration and discrimination measurement. It will help to further comparison of SCORE model performance in Canada with other European countries and will facilitate the recalibration of the SCORE model in the local Canadian context as done in other European countries.

The presence of family history of premature CVD (103) and obesity (35) are considered as very important CVD risk factors. Obesity in Canada is on the rise, so it would be interesting to further evaluate their possible addition in the SCORE model for the prediction of fatal CVD.

Finally, considering the multi-ethnic society of Canada and based on the evidence that CVD mortality varies among people from different ethnic origins, exploring the possibility of recalibrating the SCORE model taking ethnic origin into consideration is also suggested.

An absolute risk of 5% has been suggested as a cut-off point for identifying people at high-risk of having CVD by the SCORE project researchers and European guideline on cardiovascular prevention has also suggested this cut-off margin for providing treatment to the high-risk individual. But considering the gradual declining prevalence of CVD mortality, nowadays people with such high-risk particularly in the western world is low. Researchers are proposing reconsideration of this arbitrary cut-off point; Dutch 2006 guideline suggested a 10% cut-off point for treatment based on cost effectiveness and a limited capacity of healthcare workers (104). Considering the low-risk situation in Canada, this proposal may also be explored as a future research in Canada.

Appendices

Appendix 01: SPSS syntax for estimating 10-year CVD risk in male: SCORE high-risk model

The coefficients which are used in the syntax are taken from Table A and B given on page 39.

WEIGHT BY pwtgc.

USE ALL.

COMPUTE filter_\$=(CHD_all_mortality = 1).

VARIABLE LABELS filter_\$ 'CHD_all_mortality = 1 (FILTER)'.
VALUE LABELS filter_\$ 0 'Not Selected' 1 'Selected'.

FORMATS filter_\$ (f1.0).

FILTER BY filter_\$.

EXECUTE.

*******STEP 1 -High_male_CHD**

compute HMsurgave=0.

compute HMsurgave=exp(-(exp(-21.0))*(age-20)**4.62).

compute HMsurgave10=exp(-(exp(-21.0))*(age-10)**4.62).

******STEP 2 - High_male_CHD**

compute HMw=0.

compute HMw=0.24*(tchol-6)+0.018*(msys-120)+0.71*(cursmoke).

******STEP 3 -High_male_CHD**

compute HMsage=0.

compute HMsage=(HMsurgave)**exp(HMw).

compute HMsage10=(HMsurgave10)**exp(HMw).

******STEP 4 -High_male_CHD**

compute HMs10age=0.

compute HMs10age=HMsage10/HMsage.

*******STEP 5 -High_male_CHD**

compute HMrisk10CHD=1-HMs10age.

*******selection of Male non-chd**


```

USE ALL.
COMPUTE filter_$=(NCHD_all_mortality = 1).
VARIABLE LABELS filter_$ 'NCHD_all_mortality = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.

*****STEP 1 - High_male_NON-CHD
compute HMncsurvage=0.
compute HMncsurvage=exp(-(exp(-25.7))*(age-20)**5.47).
compute HMncsurvage10=exp(-(exp(-25.7))*(age-10)**5.47).

*****STEP 2 -- High_male_NON-CHD
compute HMncw=0.
compute HMncw=0.02*(tchol-6)+0.022*(msys-120)+0.63*(cursmoke).

*****STEP 3 -- High_male_NON-CHD
compute hfncsage=0.
compute HMncsage=(HMncsurvage)**exp(HMncw).
compute HMncsage10=(HMncsurvage10)**exp(HMncw).

*****STEP 4 -- High_male_NON-CHD
compute HMncs10age=0.
compute HMncs10age=HMncsage10/HMncsage.

*****STEP 5 -- High_male_NON-CHD
compute HMncrisk10NCHD=1-HMncs10age.
FILTER OFF.
USE ALL.
EXECUTE.

***** STEP 6
Compute highMale_CVDRISK=HMrisk10CHD+HMncrisk10NCHD.
compute highMale_RISKPERCENT=highMale_CVDRISK*100.
freq var= highMale_RISKPERCENT.
EXECUTE.

```

**Appendix 02: SPSS syntax (SPSS 23) for estimating 10-year CVD risk in female:
SCORE low-risk model**

The coefficients which are used in the syntax are taken from Table A and B given on page 39.

WEIGHT BY pwgtc.

USE ALL.

COMPUTE filter_\$=(CHD_all_mortality = 1).

VARIABLE LABELS filter_\$ 'CHD_all_mortality = 1 (FILTER)'.
VALUE LABELS filter_\$ 0 'Not Selected' 1 'Selected'.

FORMATS filter_\$ (f1.0).

FILTER BY filter_\$.

EXECUTE.

*****STEP 1 - Low Risk female CHD

compute Lfsurva=0.

compute Lfsurva=exp(-(exp(-29.8))*(age-20)**6.36).

compute Lfsurva10=exp(-(exp(-29.8))*(age-10)**6.36).

*****STEP 2 - Low Risk female CHD

compute Lfw=0.

compute Lfw=0.24*(tchol-6)+0.018*(msys-120)+0.71*(cursmoke).

*****STEP 3 - Low Risk female CHD

compute Lfsage=0.

compute Lfsage=(Lfsurva)**exp(Lfw).

compute Lfsage10=(Lfsurva10)**exp(Lfw).

*****STEP 4 - Low Risk female CHD

compute Lfs10age=0.

compute Lfs10age=Lfsage10/Lfsage.

*****STEP 5 - Low Risk female CHD

compute Lfrisk10CHD=1-Lfs10age.

*****selection of non-chd

```

USE ALL.
COMPUTE filter_$=(NCHD_all_mortality = 1).
VARIABLE LABELS filter_$ 'NCHD_all_mortality = 1 (FILTER)'.
VALUE LABELS filter_$ 0 'Not Selected' 1 'Selected'.
FORMATS filter_$ (f1.0).
FILTER BY filter_$.
EXECUTE.

*****STEP 1 - Low Risk female NON-CHD
compute Lfnctsurvage=0.
compute Lfnctsurvage=exp(-(exp(-31.0))*(age-20)**6.62).
compute Lfnctsurvage10=exp(-(exp(-31.0))*(age-10)**6.62).

****STEP 2 --Low Risk female NON-CHD
compute Lfnctw=0.
compute Lfnctw=0.02*(tchol-6)+0.022*(msys-120)+0.63*(cursmoke).

****STEP 3 --Low Risk female NON-CHD
compute Lfnctage=0.
compute Lfnctage=(Lfnctsurvage)**exp(Lfnctw).
compute Lfnctage10=(Lfnctsurvage10)**exp(Lfnctw).

****STEP 4 --Low Risk female NON-CHD
compute Lfnct10age=0.
compute Lfnct10age=Lfnctage10/Lfnctage.

*****STEP 5 --Low Risk female NON-CHD
compute Lfnctrisk10NCHD=1-Lfnct10age.
FILTER OFF.
USE ALL.
EXECUTE.

**** STEP 6 - Low Risk female CHD and NON-CHD
Compute Lowf_CVDRISK=Lfnctrisk10CHD+Lfnctrisk10NCHD.
compute Lowf_RISKPERCENT=Lowf_CVDRISK*100.
freq var= Lowf_RISKPERCENT.
EXECUTE.

```

Appendix 03: Standardized all-cause and CVD mortality rates - CHHS Follow-up Study

Canadian 1991 population was taken as standard population

Province	All-cause Mortality				CVD Mortality		
	Person-years	Deaths	Crude Rate	Standardized Rate*	Deaths	Crude Rate	Standardized Rate*
Manitoba	10364250	65548	6.3	6.72	19502	1.88	2.01
Saskatchewan	9170156	65190	7.11	7.37	21812	2.38	2.48
Alberta	22889335	118260	5.17	6.39	41909	1.83	2.37
All	42423741	249001	5.87	6.74	83225	1.96	2.31

* Age-sex standardized rate per 1000 population.

* Crude and standardized death rate for all-cause mortality and CVD mortality were done for population of 20-74 years old

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Sex	Province	All-cause Mortality				CVD Mortality		
		Person-years	Deaths	Crude Rate	Standardized Rate*	Deaths	Crude Rate	Standardized Rate*
Male	Manitoba	5052282	36533	7.23	7.69	11520	2.28	2.41
	Saskatchewan	4532008	39171	8.64	8.69	12853	2.84	2.85
	Alberta	11382183	67243	5.91	7.75	29455	2.59	3.45
	All	20966473	142949	6.82	7.95	53827	2.57	3.05
Female	Manitoba	5311968	29017	5.46	5.78	7984	1.50	1.62
	Saskatchewan	4638148	26017	5.61	5.95	8959	1.93	2.01
	Alberta	11507152	51018	4.43	5.28	12455	1.08	1.39
	All	21457268	106053	4.94	5.62	29399	1.37	1.61

* Age-sex standardized rate per 1000 population.

* Crude and standardized death rate for all-cause mortality and CVD mortality were done for population of 20-74 years old

Appendix 04: Standardized all-cause and CVD mortality rates - CHHS Follow-up Study

1991 population from Manitoba, Saskatchewan and Alberta were taken as standard population

Province	All-cause Mortality				CVD Mortality		
	Person-years	Deaths	Crude Rate	Standardized Rate*	Deaths	Crude Rate	Standardized Rate*
Manitoba	10364250	65548	6.32	6.51	19502	1.88	1.95
Saskatchewan	9170156	65190	7.11	7.15	21812	2.38	2.40
Alberta	22889335	118260	5.17	6.15	41909	1.83	2.29
All	42423741	249001	5.87	6.51	83225	1.96	2.24

* Age-sex standardized rate per 1000 population.

* Crude and standardized death rate for all-cause mortality and CVD mortality were done for population of 20-74 years old

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Sex	Province	All-cause Mortality				CVD Mortality		
		Person-years	Deaths	Crude Rate	Standardized Rate*	Deaths	Crude Rate	Standardized Rate*
Male	Manitoba	5052282	36533	7.23	7.53	11520	2.28	2.34
	Saskatchewan	4532008	39171	8.64	8.50	12853	2.84	2.80
	Alberta	11382183	67243	5.91	7.52	29455	2.59	3.39
	All	20966473	142949	6.82	7.75	53827	2.57	2.98
Female	Manitoba	5311968	29017	5.46	5.56	7984	1.50	1.57
	Saskatchewan	4638148	26017	5.61	5.74	8959	1.93	1.92
	Alberta	11507152	51018	4.43	5.06	12455	1.08	1.33
	All	21457268	106053	4.94	5.39	29399	1.37	1.55

* Age-sex standardized rate per 1000 population, * Crude and standardized death rate for all-cause mortality and CVD mortality were done for population of 20-74 years old

Appendix 05: Standardized all-cause and CVD mortality rates - CHHS Follow-up Study

Canadian 2000 population were taken as standard population

Province	All-cause Mortality				CVD Mortality		
	Person-years	Deaths	Crude Rate	Standardized Rate*	Deaths	Crude Rate	Standardized Rate*
Manitoba	10364250	65548	6.3	7.13	19502	1.88	2.13
Saskatchewan	9170156	65190	7.1	7.76	21812	2.38	2.59
Alberta	22889335	118260	5.2	6.69	41909	1.83	2.45
All	42423741	249001	5.87	7.09	83225	1.96	2.41

* Age-sex standardized rate per 1000 population.

* Crude and standardized death rate for all-cause mortality and CVD mortality were done for population of 20-74 years old

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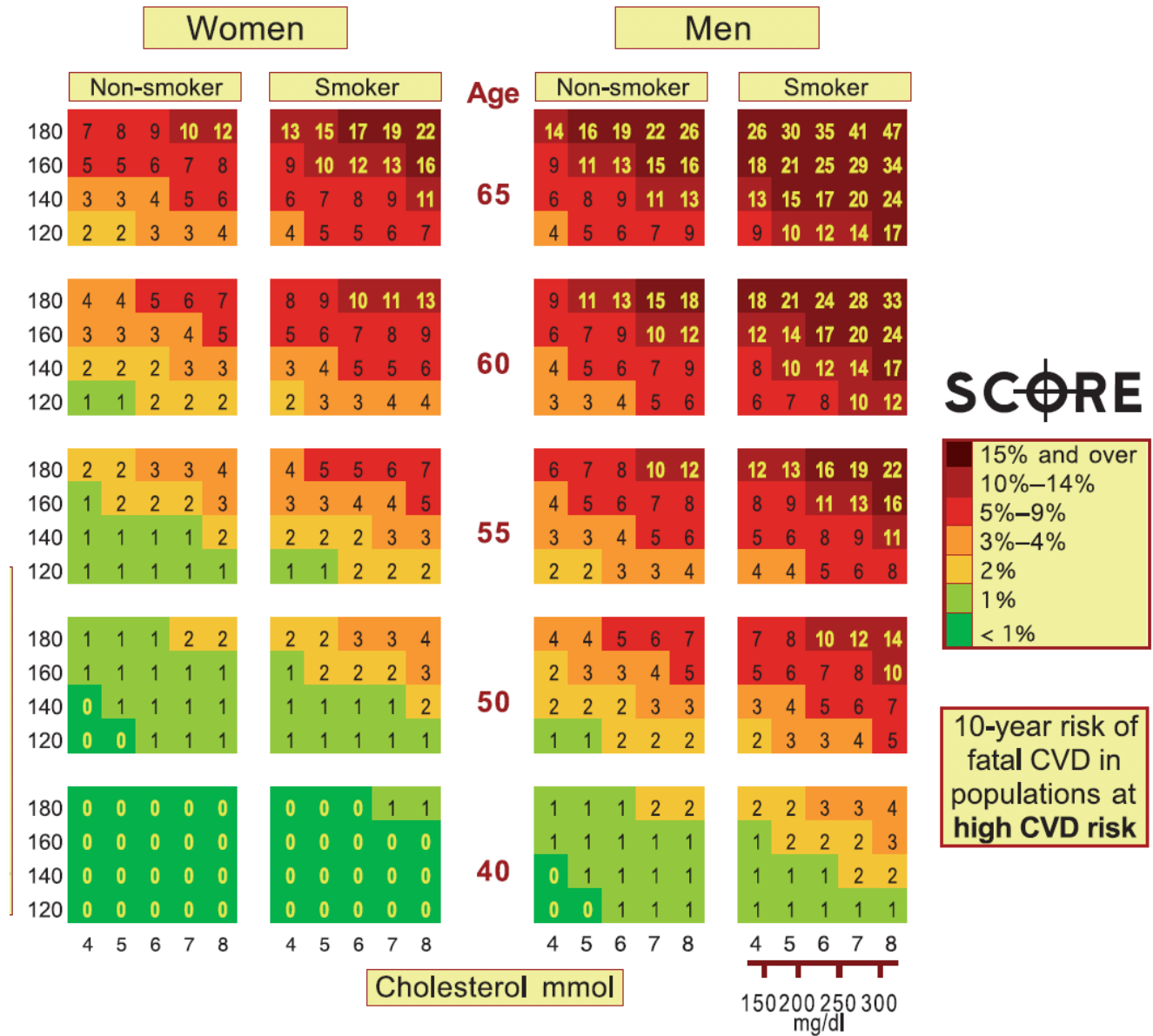
Sex	Province	All-cause Mortality				CVD Mortality		
		Person-years	Deaths	Crude Rate	Standardized Rate*	Deaths	Crude Rate	Standardized Rate*
Male	Manitoba	5052282	36533	7.2	8.29	11520	2.28	2.5
	Saskatchewan	4532008	39171	8.6	9.40	12853	2.84	3.04
	Alberta	11382183	67243	5.9	8.14	29455	2.59	3.65
	All	20966473	142949	6.8	8.47	53827	2.57	3.25
Female	Manitoba	5311968	29017	5.5	6.05	7984	1.50	1.68
	Saskatchewan	4638148	26017	5.6	6.08	8959	1.93	2.04
	Alberta	11507152	51018	4.4	5.55	12455	1.08	1.41
	All	21457267.99	106053	4.9	5.85	29399	1.37	1.65

* Age-sex standardized rate per 1000 population.

* Crude and standardized death rate for all-cause mortality and CVD mortality were done for population of 20-74 years old

Appendix 06: SCORE risk chart (high-risk version) adopted from SCORE 2003 article¹⁶

10 year risk of fatal CVD in high-risk regions of Europe by gender, age, systolic blood pressure, total cholesterol and smoking status



Risk is read by rounding the person's age to the nearest age shown on the chart, their cholesterol level the nearest whole unit, and their blood pressure to the nearest multiple of 20 mmHg.

Appendix 07: Baseline characteristics of the CHHS population (40-65 years)

**Summary of baseline risk factor levels in the CHHS Follow-up Study population,
age group 40-65 years**

	Male	Female
Age	50.8 (± 7.6)	51.6 (± 7.5)
SBP (mm Hg)	127.5 (± 14.8)	123.6 (± 16.6)
TC (mmol/L)	5.4 (± 0.93)	5.3 (± 0.96)
Smoking (%)	29%	23.7%

** Results are expressed as weighted value of mean \pm standard deviation or as weighted percentages (%),
SBP: Systolic Blood Pressure, TC: Total Cholesterol*

Appendix 08: Letter from STATA Corporation on ROC analysis

Stata Technical Support <tech-support@stata.com>

Mon 12/1/2014 11:50 AM

Inbox

To: Afza, Ruh;

Dear Ruh,

Currently, none of Stata's commands that calculate the area under an ROC curve and the confidence interval are able to accept sampling weights (i.e. pweights). However, you can use the `-lroc-` command following `-logistic-` to compute the area under the curve. Notice that you must specify the dependent variable and `-beta-` option in when you use pweights. Here is an example.

```
sysuse auto, clear
logistic for mpg [pw=turn]
mat b = e(b)
lroc for, beta(b)
```

Sincerely,

Rose

Rose Medeiros, Ph.D.

Senior Statistician, StataCorp LP

tech-support@stata.com

You wrote:

Hi,

I am using a complex survey data for doing my MSC thesis. I need to do a ROC of "10 years predicted absolute risk" and the "observed 10 years death". We got the absolute risk variable using "SCORE equation" (ref: Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003; 24:987-1003) based on a survival analysis.

But now I need to use this "absolute risk" variable and the "observed death" variable to create a ROC curve and to see the AUC for goodness of fit. I tried to do it by using STATA but it does not allow to take pweight rather ask for frequency weight. Since I have pweight (survey weight), I need to weight cases for doing the ROC. Could you please help me in this regard by sending the SYNTAX and reference.

Looking forward to your reply.

Thanks and regards,

Ruh Afza

MSC 2nd year, Department of Community Health and Epidemiology

University of Saskatchewan

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