THE MODIFYING EFFECT OF AGING AND TRACKING ON RISK FACTORS FOR ISCHEMIC HEART DISEASE IN THE MANITOBA FOLLOW-UP STUDY

BY

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A Thesis
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DOCTOR OF PHILOSOPHY

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THE UNIVERSITY OF MANITOBA

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Robert Bruce Tate

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ABSTRACT

The Manitoba Follow-up Study is a prospective cohort study of 3,983 initially healthy, male, aircrew recruits from the Royal Canadian Air Force during World War II. These men have been followed since 1948 with periodic routine medical examinations. The extent to which aging might modify the distributions and effects of risk factors for ischemic heart disease (IHD) was examined in this thesis.

Over a 45-year follow-up period 1,098 men developed IHD at a mean age of 60 years. First IHD events were documented in 47% as myocardial infarction (MI), 41% angina pectoris (AP) and 12% sudden death (SD). The incidence of IHD increased with age. Mean and variance of systolic blood pressure (SBP) and diastolic blood pressure (DBP) increased with age to 60 years; SBP continued to increase and DBP plateaued there after. Mean body mass index (BMI) increased with age, and levelled off at 60 years. The biological tendency for a repeated measurement of an individual to maintain its distributional position relative to others over time is called tracking. Utilising the longitudinal nature of this study, with examinations selected at 5-year intervals between 30 and 75 years of age, strong evidence for tracking of SBP, DBP and BMI was apparent. Tracking was greatest in subjects between 30 and 50 years of age and greater for BMI compared to either blood pressure. Using Cox proportional hazard models, the age-specific effects of these risk factors varied with manifestation of IHD. The relative risk of IHD for blood pressure and smoking declined with age, while the relative risk associated with BMI and presence of diabetes mellitus did not change with age.

Individual characterisations of tracking based on the regression of percentiles of SBP, DBP and BMI on age contributed to models of IHD at age 50, 60 and 70 years, in addition to risk factor measurements at those ages.

The dynamic relationship between age and risk factors for IHD, with respect to distributions, magnitude of effect, relative importance and patterns evolving from repeated measurement should be important considerations when planning primary preventive strategies for IHD.

DEDICATION

This thesis is dedicated to

the memory of Dr. F. A. L. Mathewson

and

the 3,983 members of

The Manitoba Follow-up Study

ACKNOWLEDGEMENT

While this thesis is dedicated to the memory of Dr. F. A. L. Mathewson, it is with sincere admiration that I further acknowledge his foresight in the design and his determination in the execution leading to the success of the Manitoba Follow-up Study.

My thanks goes to Drs. T.K. Young and T.H. Hassard, the members of my advisory committee from the Department of Community Health Sciences for their guidance. During the early years of the Study, my external advisor, Dr. T.E. Cuddy, then a young medical student, was employed by Dr. Mathewson. Dr. Cuddy returned forty years later to succeed Dr. Mathewson as the Medical Director of the Study. His mentorship in cardiology and insight in cardiovascular research throughout my student life was invaluable. At every step of my doctoral research, Dr. Jure Manfreda, my advisor, has challenged me with his critical review. After many hours of thinking and rethinking his comments, I believe a better product has emerged. Thank you, Jure.

Brenda, and our sons, Andy and Kevin, permitted me the time and opportunity to pursue this doctoral program. Without their love and unwavering support over the past five years, I would not have succeeded. Thank you all, from the bottom of my heart.

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LIST OF ABBREVIATIONS

AP	angina pectoris
BMI	body mass index
bmi%ile	body mass index percentile
CHD	coronary heart disease
CVD	cardiovascular disease
DBP	diastolic blood pressure
dbp%ile	diastolic blood pressure percentile
DM	diabetes mellitus
df	degrees of freedom
HDL	high density lipoprotein
ID	incidence difference
IHD	ischemic heart disease
IR	incidence ratio
kg/m^2	kilograms per meter squared
LDL	low density lipoprotein
LVH	left ventricular hypertrophy
MFUS	Manitoba Follow-up Study
MI	myocardial infarction
mm Hg	millimeters of mercury

PH	proportional hazards
pyrs	person years
Q1	bottom quintile, all percentiles below 20
Q2	second from bottom quintile, percentiles between 20 and 39
Q3	middle quintile, percentiles between 40 and 59
Q4	second from top quintile, percentiles between 60 and 79
Q5	top quintile, all percentiles 80 and above
RCAF	Royal Canadian Air Force
SBP	systolic blood pressure
sbp%ile	systolic blood pressure percentile
SD	sudden death
SMR	standardized mortality ratio
SES	socioeconomic status
T1	bottom tertile, all percentiles below 33
T2	middle tertile, percentiles between 33 and 67
T3	top tertile, all percentiles above 67
WWII	World War Two
%ile	percentile
χ^2	chi square
95% CI	95 percent confidence interval

1 INTRODUCTION

Since the end of World War Two (WWII), the precursors and prognosis of cardiovascular disease have been a major subject of medical investigations. Prospective population studies have been initiated, risk factors recorded and the development of disease documented. Although a host of factors have been identified as associated with heart disease it is generally agreed that elevated blood pressure, high serum cholesterol levels and smoking are the three main responsible, and modifiable, risk factors for ischemic heart disease. Statistical models have been developed to identify and estimate the magnitude of effect that individual factors or groups of factors have on the likelihood of disease. Risk factors have been able to account for a large percent of all coronary heart disease. Through risk factors, 60% of coronary heart disease can be identified in 20% of the population (Kannel and Schatzkin 1983, Epstein 1995). Thus, there is considerable room for improvement in identifying other characteristics for this prediction.

Terminology for referring to heart disease is not strictly standardized. In this thesis, ischemic heart disease (IHD) is defined by evidence of angina pectoris (AP), myocardial infarction (MI) or sudden death (SD). Coronary heart disease (CHD) refers to disease of the heart and diseases related to blood supply to the heart, and hence includes IHD as defined as well as death attributed to IHD (Health and Welfare Canada 1995). Cardiovascular disease (CVD) is defined by the Heart and Stroke Foundation of Canada to include all diseases of the circulatory system defined by ICD-9 codes 390 through 459.

These codes include acute myocardial infarction, ischemic heart disease, valvular heart disease, peripheral vascular disease, arrhythmias, high blood pressure and stroke. As such, cardiovascular disease is the widest definition encompassing aspects of diseases of the heart as well as diseases of the vascular systems. While the objectives of this thesis will focus on IHD, much of the discussion from other studies relates to cardiovascular disease in general.

1.1 Population Studies of Cardiovascular Disease

An era of modern investigation into cardiovascular disease began at the end of WWII. The World Health Organization's initiatives in 1948 set the stage for the development of population studies in the next few years. In 1949, the National Heart Institute was established to promote medical research in the United States. In North America, two long standing prospective cohort studies designed to investigate cardiovascular disease were initiated in 1948. One was in the USA, the Framingham Study (Dawber 1980), and the other in Canada, the Manitoba Follow-up Study (Mathewson and Varnam 1960). The former established a cohort of 5,127 men and women age 35 to 62 years, all residents of Framingham, Massachusetts. The latter enlisted a cohort of 3,983 healthy young male air crew recruits from the Royal Canadian Air Force in WWII. During the 1950's these population studies would, for the first time, follow a fixed cohort of healthy people, with routine measurements and medical tests. As disease developed in the subjects of these cohorts, evidence would be documented.

Further, the design of these studies would permit the prospective documentation of medical events until death. Careful record keeping made possible some of the first prospective medical reports of disease, particularly cardiovascular disease, as it developed in aging populations. These two studies both continue today, each having just celebrated fifty years of existence. They share a distinction of being the longest continuously running cohort studies ever undertaken in the world.

During the 1950's and 1960's research groups in the USA and Europe would add to a growing base of population studies. Middle aged white American males from five cohorts, the Albany Civil Servant study, the Chicago Peoples study, Chicago Western Electric Company, the Tecumseh Community Study and the Framingham study were merged for analysis in 1964. This formed one large cohort of 12,381 men aged 40 to 59 years with an average of 8 years of follow-up. This endeavor, called The Pooling Project (The Pooling Project Research Group 1978) was the first major population study to be able to refine with some degree of assurance, the predictive indices for manifestations of "major coronary events", defined as nonfatal or fatal myocardial infarction and coronary deaths. Measurements of serum cholesterol, blood pressure and cigarette use, recorded at a single examination of adult American men, (were) shown to be highly indicative of first heart attack over the next decade (The Pooling Project Research Group 1978). The Seven Countries Study (Keys 1980) began in 1958 to examine reasons for regional variation in rates of cardiovascular disease. Within a very short time, by the early 1960's, enough

data had been collected to permit statements about associations of factors with atherosclerosis and heart disease.

Most cohort studies were designed to prospectively examine cardiovascular disease mortality and morbidity. Mortality proved easier to monitor through linkages with existing sources of vital statistics data routinely compiled for administrative purposes. Morbidity monitoring was more labour intensive for most studies because of the necessity for contact and re-examination of cohort subjects to determine evidence of disease. Studies have reported on all cause mortality, as well as death due to cardiovascular and non-cardiovascular causes.

1.2 Risk Factors and cardiovascular disease

In a 1961 report, Dr. William Kannel, director of the Framingham Study, coined the phrase "risk factor" (Kannel et al. 1961). The concept of risk associated with a factor and its relationship to cardiovascular disease should be defined with consideration for the strength of the association between the two (statistical significance), the direction of the association (causality), consistency of the association and societal impact.

Very quickly serum cholesterol, blood pressure and smoking were reported as risk factors causally related to coronary heart disease. A 1981 literature review identified 246 risk factors for coronary heart disease (Hopkins and Williams 1981). Albeit the criterion for inclusion of a factor in this report was the finding in one publication of the description of an association, either positive or negative, with coronary heart disease, this report

highlights the outburst of activity in cardiovascular research over a period of perhaps thirty years. Risk factors were grouped in categories as demographic, environmental exposures, lifestyle/psychosocial, physical/biomedical, serum measurements, platelet/coagulation factors, coexisting medical conditions, dietary excesses, dietary deficiencies, and drug liabilities. Risk factors were classified by evidence for association and suggested mechanisms as initiators, promoters, potentiators and precipitators for coronary heart disease. Determination of the most important risk factors, was described as an "onerous task", but it was concluded that this systematic approach may be helpful as a starting point.

Cardiovascular risk factors can be broadly grouped as major or minor risk factors (Stamler 1995). Major risk factors are those that are highly prevalent, causally associated with high risk of coronary disease and potentially avoidable or reversible. For example, smoking and hypertension are both highly prevalent in our population and have been shown to be strongly related to heart disease and can be controlled or stopped, hence both are major risk factors. Diabetes mellitus (DM) is both controllable and strongly associated with heart disease in our population, but not as highly prevalent, hence it is not considered a major risk factor. Although age and male gender are highly associated with cardiovascular disease, neither is reversible. Hence, age and gender are not considered major risk factors.

There are three universally accepted major risk factors for cardiovascular disease: high blood pressure, high blood cholesterol and smoking. Health Canada identifies

sedentary lifestyle, overweight and diabetes as other important risk factors (Health and Welfare Canada 1995). Implicated with these are the roles of many other factors, including aging, gender, diet and familial history of cardiovascular disease. Other social and economic factors measured in many populations by income, education or occupation have been shown to be related to health in general, as well as to some extent with cardiovascular health (Kaplan and Keil 1993).

1.3 An overview of the Manitoba Follow-up Study

During WWII, Dr. F.A.L. Mathewson was responsible for the examination of approximately 7,000 male recruits to evaluate their fitness for RCAF air crew training in Toronto and Edmonton. Examinations included physical measurement of height, body weight and blood pressure, medical history of past illnesses and the recording of a resting electrocardiogram. Contact with the post-war survivors was sought between 1946 and 1948 and each man located was invited to take part in a longitudinal study aimed at the prospective evaluation of the prognostic significance of electrocardiographic changes as they would develop in an otherwise healthy male.

Initiated on July 1, 1948, the Manitoba Follow-up Study (MFUS) has become Canada's longest running prospective investigation of cardiovascular disease. An examination of all study members at entry comprised the baseline examination. Since then, the cohort of 3,983 healthy, young, men has been followed continuously with annual contact and regularly scheduled medical examinations. Routine medical

examinations administered by each study member's personal physician have been requested at five-year intervals until the mid 1960's and at three-year intervals since. Medical examinations include a general cardiovascular assessment, blood pressure and body build measurement and a resting 12 lead electrocardiogram.

In the early years of the study, a return postcard was mailed annually to each study member to maintain contact and confirm addresses. Since 1978, a one page annual questionnaire has been sent to determine intercurrent illnesses or hospitalisations and thus permit a timely follow-up of medical events between routine examinations. This annual questionnaire also serves to monitor vital status. Periodically, more extensive mailed questionnaires have been used to obtain additional information, retrospectively, on smoking habits, family history of cardiovascular disease, physical activity, occupational profiles and perceived level of stress during the war.

After 45 years of follow-up, to July 1, 1993, the vital status of 96% of the cohort was known; only 4% of the cohort had been lost to follow-up. Clinical evidence of IHD, including myocardial infarction, angina pectoris and sudden death has been documented in 1,098 (27%) subjects. The mean age of the 2,292 men alive was 74 years and the mean age at death of the 1,691 decedents was 64 years. While the mortality rate of the MFUS cohort is lower than the mortality experience of the Canadian male population, the distribution of cause of death of deceased study members is similar to that of all Canadian males.

1.4 General Objectives

The epidemiology, i.e. frequency, distribution and determinants of IHD in men can be best examined with a prospectively compiled longitudinal database. It is proposed in this thesis to use the MFUS database to examine the extent to which the effects of recognised risk factors for IHD: elevated blood pressure, smoking, body build and diabetes mellitus are modified by aging. Analysis of these risk factors for IHD showed a declining effect blood pressure and smoking with age (Tate et al. 1996, Tate et al. 1998). The prognostic significance and relative importance of these risk factors has been shown to vary for manifestations of IHD at different ages (Tate et al. 1997b).

When a characteristic of an individual is measured repeatedly over time, the biologic phenomenon for the values of the characteristic to maintain a stable position relative to others in the population is called tracking. The degree to which blood pressure and body mass index (BMI) measurements track with age will be examined in this thesis. In a recent analysis of blood pressure tracking over a 40 year period of the MFUS cohort, it was reported that tracking was strong both for subjects in the highest and lowest quintile of the systolic (SBP) and diastolic blood pressure (DBP) distributions (Tate et al. 1995b). Evidence for tracking was particularly strong between ages 30 and 50 years over intervals of up to 20 years. It is anticipated that tracking of body mass index may be at least as strong as reported for blood pressure.

Tracking indices for a characteristic in a population are defined on the basis of the predictability of the characteristic over time. Because of the longitudinal nature of

MFUS, it will be possible to identify men whose blood pressure or body build tracks from young to middle age, and whether these men subsequently have patterns of development of IHD in later life that differ from those men whose measurements do not track. Previous analysis has suggested that those with SBP that tracked strongly at higher levels from age 40, 45 and 50 years, had a greater risk of IHD morbidity and IHD mortality compared to those whose blood pressure did not track (Tate et al. 1997a).

At the individual level, using serial measurements, patterns of blood pressure or body build with age can be defined in terms of the slope and variability of the regression of blood pressure or body build on age. It may be that these regression line parameters define subjects at varying risk of IHD. Fitting models with these characteristics derived from the longitudinal observation of risk factors in individuals may provide further insight into the relationship between tracking of these measurements and IHD risk. Thus, the importance of the effect of tracking of blood pressure and body build may have on the development of all IHD as well as on each manifestation of IHD; myocardial infarction, angina pectoris and sudden death will be examined. The additional contribution of tracking to the prediction of IHD may identify high risk individuals at younger ages.

1.5 Specific Objectives

IHD is an important health problem in our society and continues to be a major cause of morbidity and mortality. Consequently, the identification of factors associated with IHD and quantification of levels of risk is of ongoing interest. The risk factor

profile for IHD as well as the magnitude of effect and relative importance of risk factors for IHD may be changing with age. This dynamic relationship must be kept in mind when planning strategies for prevention of cardiovascular disease.

Many recent analyses of the MFUS data base have been directed at the epidemiology of IHD. Some aspects of that research are proposed as objectives of this thesis. This doctoral thesis will draw upon the knowledge from the earlier research undertaken in this field of study and bring together a collective analysis of the modifying effects of aging and tracking (Tate et al. 1995b) on traditional risk factors for IHD (Tate et al. 1998). It is proposed in this thesis to analyze data from 45 years of follow-up (between July 1, 1948 and June 30, 1993) of the MFUS to address the following five specific objectives:

1. To determine the age-specific incidence of ischemic heart disease and each of its manifestations: myocardial infarction, angina pectoris and sudden death in the MFUS cohort.

2. To examine the extent to which the distributions of recognised risk factors: systolic blood pressure, diastolic blood pressure, body mass index, diabetes and smoking are changing with age.

3. To determine the extent to which systolic blood pressure, diastolic blood pressure and body mass index measurements track with advancing age.

4. To determine the extent to which the effects of recognised risk factors, i.e. elevated blood pressure, body mass index and diabetes mellitus and smoking, for incident ischemic heart disease and its manifestations are modified by aging.

5. To determine the extent to which tracking of systolic blood pressure, diastolic blood pressure and body mass index contribute to models of incident ischemic heart disease and its manifestations.

2 A HISTORY OF THE MANITOBA FOLLOW-UP STUDY

2.1 About Dr. F.A.L. Mathewson (1905-1994)

The history of the Manitoba Follow-up Study cannot be told without first providing an introduction to and appreciation for the man responsible for the inception, motivation and diligent persistence behind it. Francis Alexander Lavens Mathewson was born in 1905 in New Westminster BC and moved to Winnipeg with his family at a young age. He attended medical school at the University of Manitoba and graduated with an M.D. degree in the Class of 1931 and with a B.Sc. (Medicine) degree in 1933. Dr. Mathewson began a private practice in Winnipeg and was appointed to the medical faculty at the University of Manitoba. As a physician at the Winnipeg General Hospital from 1935 to 1975, he was director of the electrocardiography department from 1957 to 1975.

Dr. Mathewson served in Royal Canadian Air Force (RCAF) during WWII as the deputy director of Medical Services (Professional). He also served with the Committee on Aviation Medical Research and with the war over in 1945, he maintained ties with the RCAF, but returned to teaching at the University of Manitoba and to his private practice with interest in cardiology, and specifically, electrocardiography.

Dr. Mathewson was a founding member and served as President of the Canadian Cardiovascular Society (1957-1958). He also served as President of the Canadian Life

Insurance Medical Officers Association (1955-1956) and of the Association of Life Insurance Medical Directors of America (1968-1969).

Throughout his career he maintained other interests apart from medicine, as a Manitoba historian, particularly of the influence of the Hudson Bay Company in Western Canada. He was a naturalist, enjoying wildlife photography. As a driving force behind the creation of the Museum of Man and Nature in Winnipeg, the Mathewson Reading Room was created there in his honour, following his death in 1994.

2.2 Origins of the Manitoba Follow-up Study

During WWII, Dr. Mathewson was in charge of the physical examination of RCAF recruits to determine their suitability for air crew training. At initial training centres in Edmonton and Toronto, the blood pressure, body weight, height, and history of childhood illness were obtained from 7,000 young Canadian men. In addition to these measurements, a resting 3 lead electrocardiogram was recorded, but not used in the screening process of candidates. During the war these electrocardiograms came up for discussion on two occasions, with Dr. Harry Ungerleider of the Equitable Life in New York, and with Sir John Parkinson in London, England. Both stressed the importance of setting up a long term study to determine the clinical significance of the electrocardiograms recorded on apparently healthy young people. (Mathewson et al. 1987). The seed that would flourish over the next fifty years was planted.

In the early years following WWII, contact was established and an invitation extended to the RCAF air crew whose electrocardiograms were on record to participate in a long term prospective investigation of cardiovascular disease. The study also included commercial air transport pilots and pilots licensed by the Ministry of Transport at that time. Although it is not precisely known how many men were drawn from each source, it is felt that except for differences in age distributions at entry to the study, these three groups were similar. On July 1, 1948 the cohort was sealed with agreement to participate having been obtained from 3,983 men. The mean age of these men was 31 years, with close to 90% between age 20 and 39 years. To my knowledge, a formal "signed consent" was never obtained, however it has been recognised that active participation implies informed consent. A letter to this regard from the Faculty Committee on the Use of Human Subjects in Research at the University of Manitoba is included as Appendix 1.

2.3 Data Collection and Management

2.3.1 Annual contact and monitoring of vital status

A medical technician training facility at the University of Manitoba Medical College was established after the war by Dr. Mathewson. The personnel "posted" there provided clerical assistance to develop a record keeping system for MFUS, "in house", apart from the RCAF files. Contact dates, current addresses and medical examination requests were manually recorded until 1985 when a personal computer database system was adopted. Initially, an annual return postcard was sent in the fall to each study

member to ascertain vital status and keep address files current. In 1978, the postcard was supplemented with a one page questionnaire, and over the next three years the postcard was phased out. Three questions are asked; 1) Have you had any new medical problem? 2) Have you had occasion to consult your Doctor? 3) Have you been admitted to hospital? (if so, where and when?). A "yes" response to any of these questions triggers a detailed review of existing records and initiates appropriate follow-up, directed to the study member, his physician or hospital.

Letters returned unopened or non responses to our correspondence were diligently followed to re-establish contact with study members. A variety of sources were used over the years including telephone, telegraph, co-operation of the aviation licensing board, physicians, next-of-kin and motor vehicle licensing departments. The follow-up process has been very successful: "During 1963 contact was established with all but five of the 3773 survivors." (Mathewson et al. 1965a); "By June 30, 1988, 40 years of follow-up (145,408 person-years of observation) had been completed, 2459 (62%) of study members were alive, 1297 (33%) died and the status of 227 (6%) was unknown." (Manfreda et al. 1992).

2.3.2 Medical examinations

Initially, medical examinations were requested from each man at five year intervals. These requests were staggered so that one-fifth of the cohort would be examined in any one year. Examination requests included measurement of height, weight, blood pressure, a general cardiovascular assessment, medication listing and a 12

lead electrocardiogram. Examinations were to be carried out by each man's own personal physician. In 1963, the protocol was altered to request examinations every three years. For some men, depending on age and type of pilot license held, records of more frequent examinations carried out by the RCAF or Department of Transport have been obtained.

A detailed coding system was developed to describe major and minor clinical findings in specific areas of interest including ischemic heart disease, cerebral vascular disease, hypertension, pulmonary vascular and peripheral vascular disease, heart murmurs, cardiac and non-cardiac surgery, diagnostic procedures as well as associated non-cardiovascular disease including cancers. Dr. Mathewson produced a coding system for the identification and classification of electrocardiographic abnormalities at about the same time as the "Minnesota Code for Coding Electrocardiographic Changes" (Blackburn et al. 1960) was being developed. The two coding systems are similar. The coding system ultimately adopted for use at MFUS identifies fifty-six areas of interest from each electrocardiogram.

2.3.3 Survey questionnaires

In 1974, a self administered mailed questionnaire was used to obtain information on smoking histories, family history of disease and occupation. A more detailed questionnaire was sent in 1982 and 1984 to update smoking and occupational information, to survey areas of physical activity and exercise detailing current activity and activity ten years prior both at work and during leisure time, to obtain information about hobbies, and to obtain place of birth and ethnic origin. The final page of the

questionnaire was a request for a narrative, asking each man to describe the most stressful experiences of his wartime experience.

2.4 Funding

MFUS was funded initially by the RCAF and the National Research Council of Canada. From the mid 1960s through to the early 1980s, the Defence Research Board, Canadian Life Insurance Officers Association and Health and Welfare Canada provided funding for operating expenses. The primary source for funding for the past 16 years, however, evolved following a 1983 Federal Health and Welfare Canada review of the study. The site review committee recommended termination of funding for primary data collection with a contingency to "wind-down" the study. The study members, themselves, said "NO", and banded together forming a committee, MUFUS-2000, to solicit funds from within the membership to continue the study. The study was established as a charitable organisation, and since 1983, the majority of the annual budget has been met by donations from the study members primarily received with replies to the yearly contact questionnaire.

2.5 Data Analysis and Publication

The peer reviewed publications from this study are listed chronologically in Appendix 2. They have been numbered for ease of reference within this section. In 1960 Dr. Mathewson's first major reports of the background to this study was published

(Appendix 2: ref 4,5), describing the mortality experience and electrocardiographic findings of the study. Therein, Dr. Mathewson outlined the prime focus of his study: "Because the suspicion of heart disease, particularly coronary artery disease, may have a far-reaching effect upon the individual, it is important to identify beyond any reasonable doubt the clinical significance of those variants that appear in the electrocardiograms of apparently healthy people." In 1965, a two part report detailed the morbidity and mortality experience, build, blood pressure and electrocardiographic findings during the first fifteen years of the study (Appendix 2 ref 7,8). A further report of the twenty year blood pressure patterns (Appendix 2 ref 9) and case series reports followed in the next ten years (Appendix 2 ref 10,11).

In the late 1970s, increased funding from the federal government, expansion in the number of staff, computerisation of medical data and recent advances in epidemiology and biostatistics all aided productivity. Since then, analyses have been undertaken in many areas. One set of reports described the relationship of blood pressure and body build to ischemic heart disease (Appendix 2 ref 12-15,20,23,28,36,38,39) and cerebrovascular disease morbidity and mortality (Appendix 2 ref 16-18). The significance of electrocardiographic findings, specifically defects in conduction and rhythm (Appendix 2 ref 19,21,22,24-27,29) have been examined. A thirty-five year "State of the Study" was published (Appendix 2 ref 32). Recently, analyses of the natural history of diseases have been published (Appendix 2 ref 31,33-35,37).

3 LITERATURE REVIEW

Since mortality statistics were first published in Canada, in 1921, cardiovascular disease has been the leading cause of death. In 1988, 41% of male and 48% of female deaths were due to cardiovascular causes. For males this included 25% due to ischemic heart disease, 7% due to strokes, and 9% due to other cardiovascular causes (Heart and Stroke Foundation of Canada 1991). While many deaths due to ischemic heart disease occur in hospital, or within a year following an acute myocardial infarction, for 12% of all men who experience ischemic heart disease sudden death is the first and only manifestation of this disease (Tate et al. 1995a).

It was estimated that in Canada in 1998, as many as 26.4 million physician visits were due to cardiovascular conditions (Heart and Stroke Foundation of Canada 1999). It is estimated that total costs to the Canadian economy, including hospital costs, physician costs, lost wages and productivity, resulting from cardiovascular disease is 17 billion dollars (Wigle et al. 1990). Cardiovascular disease is far reaching and early evidence of disease has been found in all segments of society. Even though incidence of cardiovascular disease increases rapidly with age, it is the leading cause of death in 35 to 64 year old Canadians as well. Large variations in rates of cardiovascular diseases have been found across strata of the population, both geographically and socially. However, it has been estimated that as much as 60% of all cardiovascular disease can be identified in 20% of the population (Kannel and Schatzkin 1983, Epstein 1995). Hence, it is important

to investigate factors in populations that may aid in the early identification of disease, as a first step in reducing the impact of cardiovascular disease on society.

3.1 A global perspective of cardiovascular disease

While cardiovascular disease occurs world wide, there is great geographic variation in rates of disease. Morbidity data is difficult to obtain in a standardized fashion, and most global comparisons are based on mortality. In the mid 1980's, there was a three fold difference in age standardized mortality due to cardiovascular causes in a comparison of selected countries from around the world. Japan enjoyed the lowest rate, at 170 per 100,000 with Romania almost 500 per 100,000. Canada was at the lower end in 1986 at 264 per 100,000 males (Canadian Centre for Health Information 1990). Within this spectrum, it has been observed that cardiovascular mortality rates in Central and Eastern European countries are the highest. Rates in Britain and Scandinavian countries are a little lower. Highly industrialized, wealthier countries like United States, Australia and Canada follow next. Mediterranean countries, Greece and France have lower rates, and then Japan the lowest.

These global trends of high cardiovascular disease rates have not always been the norm. In the early part of the twentieth century infectious disease was the leading cause of death worldwide. As mortality due to infectious disease was reduced, this primary cause of death in most countries was replaced by death due to chronic diseases, primarily cancer and cardiovascular disease. Developing countries today tend to have lower rates

of cardiovascular disease than developed countries. As countries develop economically, so too does the rate of cardiovascular disease increase. There are a number of possible explanations for this trend, including differences in diet, life style, prevalence of high risk activity such as smoking and physical inactivity. There is evidence however, for a decline in rates of disease to coincide with the more stable industrial economies.

While the rates of cardiovascular disease in many parts of Europe continue to rise, the rates in North America appear to have peaked in the late 1960's or early 1970's. Since that time there has been a continual decrease in mortality due to cardiovascular causes in the order of 2 percent per year. This has been a dramatic turn around from the rising rates of cardiovascular disease up until that time. This trend has been observed both for men and women. Although it was estimated in the United States that between 1980 and 1990, 25% of the decline in IHD mortality was due to primary prevention, 29% due to secondary prevention, and 46% due to improvements in treatment (Hunink 1997), unresolved issues remain around the reason(s) for this trend of decreasing mortality. Further, rates of more advanced forms of chronic heart disease, including congestive heart failure are increasing. While decreasing mortality rates may be attributed to lower incidence of disease, better management of disease at time of onset, or improving therapies and surgical interventions following disease diagnosis, with this decrease in mortality has come more physician visits, hospitalizations and hence increased cost associated with cardiovascular disease. Currently 12% of the Canadian population is age 65 years or older. It is projected that this proportion will double by the year 2040 (Heart

and Stroke Foundation 1999). With the increase in the size of the population reaching more advanced ages, and increase in more advanced disease and chronic coronary conditions, severe strains will be placed on the Canadian health care system.

3.2 Variation of cardiovascular disease in Canada

Within Canada, an East-West gradient in rates of cardiovascular disease have been reported (Health and Welfare Canada 1995). In 1988, the highest rates were at the east coast, almost 400 per 100,000 men and 270 per 100,000 women down to a low of 323 per 100,00 men and 195 per 100,00 women in British Columbia.

3.3 The pathological basis for ischemic heart disease

When the arteries supplying blood to the heart tissue are healthy, blood flows unimpeded. A critical facet of the health of arteries is the integrity and function of the inner arterial wall lining, the endothelium. Under normal functioning, lipids in the blood penetrate and move back and forth across the endothelium. If highly concentrated in the blood, lipid may become trapped and build up inside the artery between the lining and the arterial wall. The early deposits are the beginning of a process called atherosclerosis. Build up of arterial plaque may progress slowly over time and lead to narrowing of arterial walls. As the blood flow becomes restricted, less oxygen is able to reach the heart and the early stages of coronary heart disease has begun.

A restriction of oxygen supply to the heart may lead to angina pectoris on exertion. This narrowing, if severe enough, may reduce blood flow to an extent that blood supply may be completely stopped to some areas of the heart (Badimon et al. 1993). The flexibility and elasticity of the arteries that would normally ease blood flow is compromised and arteries begin to harden with plaque deposits.

Further, as the plaque lesion progress, a fissure or rupture of the lesion may occur resulting in a dislodging of the plaque from the arterial wall. The material may form a clot or plug further reducing blood flow and may result in an acute coronary syndrome, a manifest by unstable angina, myocardial infarction or sudden cardiac death. If blood flow is restricted to the heart, a myocardial infarction will occur, to the brain, a cerebral infarction or stroke may occur.

Cholesterol is a chemical in all body tissue manufactured in the liver. It is insoluble in blood and is one of a number of fatty substances called lipids attached to molecules of protein and fat that is circulated with the blood throughout the body. Cholesterol is made up of varying lipoproteins, with two basic ones being low density (LDL) and high density (HDL) lipoprotein. It is considered that higher levels of LDL may be associated with increasing plaque buildup and that the HDL type of cholesterol may in fact enhance a "cleaning" process of build up on the arterial walls. It is hence, the mixture of the two types, the ratio of the two, or the ratio of total cholesterol to HDL cholesterol that may be most useful in determining a measure of the potential for atherosclerotic harm blood lipid. In addition to the cholesterol produced normally by the

body also receives cholesterol from some of the foods we consume, ranging in higher amounts in fatty animal products to no amount of cholesterol in vegetables. For the most part, except in individuals with defective regulatory mechanisms, our body is able to regulate the amount of cholesterol normally produced, in order to compensate for the amount we consume.

The heart is the circulating pump for distribution of oxygen enriched blood, necessary to sustain life, to all parts of the body. On a continuous cycle, oxygen depleted blood enters the heart, circulates through the lungs to replenish its oxygen supply and is forced back out of the heart on the next cycle. The efficiency of this cycle is critical to health and a compromised efficiency of this process can lead to reduced blood supply, hence reduced oxygen supply, and ultimately the death of cells. The word "ischemia" is derived from the roots "isch" meaning "to restrict" and "hemo" meaning "blood", hence, ischemic heart disease, meaning disease resulting from a restriction of blood flow to the heart.

The consequences of ischemia may take many forms. Arterial narrowing may result in a restriction of blood flow, which interferes with the usual mechanical functioning of the heart. This restriction of oxygen supply to the heart may precipitate chest pain, called angina pectoris, relieved by rest or pharmaceutical intervention. More critical, is myocardial infarction, "myocardial" meaning "heart" and "infarct" literally meaning "death of cells". Myocardial infarction may present in a variety of forms, ranging from chest pain and incapacity, resulting in high short term mortality if blood

supply is not restored, to an equally critical but clinically unrecognized form, labeled "silent infarction". A lethal manifestation of ischemic heart disease, sudden death, defined by the World Health Organization as death within twenty-four hours of symptoms of ischemia, is for many persons their only manifestation of ischemic heart disease. Autopsy studies of sudden death victims have reported severe arterial narrowing.

Investigation of atherosclerosis, its progression and its possible links to cardiovascular disease have been studied since the last century. In laboratory experiments during the early part of the twentieth century, animals fed high cholesterol diets produced atherosclerotic lesions in a greater proportion than control animals. This was found not only with short term feeding of high cholesterol diets, but also for long term diet supplemented with lower levels of cholesterol. In the 1930's, populations were described where diets consisting largely of meat and dairy products were often found to have high levels of atherosclerosis. In contrast, at that time, populations like those of China and Japan, where diets were primarily vegetarian in nature, had low levels of atherosclerosis. During the depression of the 1930's when many isolated populations subsisted on low fat primarily vegetarian diets, people became lean, and levels of atherosclerosis were low. Autopsy studies of WWII soldiers from European countries having lived through the depression showed similar findings of low atherosclerotic levels. This was even more apparent for civilians who had lived with low food supplies.

3.4 Risk factors for cardiovascular disease

3.4.1 High blood pressure

Strong evidence exists that a continuum of increasing risk for cardiovascular disease is associated with increasing level of blood pressure (Stamler et al. 1993a, Labarthe 1998). The role of increased blood pressure leading to cardiovascular disease may be that the direct force of blood against arterial walls causes damage to the cells of the arterial wall lining, allowing more entry points for plaque deposit buildups. Further, the stronger force of blood flow may result in the loss of elasticity of the arteries, and weaken the endothelium.

Increased risk has been shown whether systolic, diastolic or pulse pressure is examined (Stamler et al. 1993a). Increased risk is apparent in most societies and for both males and females. Although optimal levels of blood pressure are generally thought of as systolic pressure below 120 mm Hg and diastolic blood pressure below 80 mm Hg (Stamler et al. 1993a), clear definitions of "hypertension" are unnecessary from the perspective of defining risk. Definition of hypertension is important, however, from the point of view of antihypertensive treatment, or control of high blood pressure. Hypertension defined as a diastolic blood pressure equal to or greater than 90 mm Hg, or being treated with medication, a salt-restricted diet or weight reduction program, identified 15% of the Canadian population (Health and Welfare Canada 1995). This prevalence ranged from 5% in those aged 18 to 34 years, 21% at ages 35-64 years, and 34% at ages 65 to 74 years. It was estimated that in Canada as many as 25% of adults

with these levels may not know they are hypertensive (Joffres et al. 1992). Pharmaceutical control of high blood pressure, targeted mainly at elevated diastolic blood pressure, is available and has been shown to be effective at all elevated levels in reducing blood pressure. Lifestyle modifications including weight control, limiting alcohol consumption and salt intake, regular exercise and control of stress are all recommendations of a recent review of non-pharmaceutical hypertension management options (Campbell et al. 1999).

Blood pressure has been shown to increase with age, possibly reflecting higher arterial resistance resulting from loss of arterial wall elasticity common with aging. Limits defining normal blood pressure levels, or hypertension, may need to be adjusted to reflect the shift in the blood pressure distribution with age. In Western populations (Collins and MacMahon 1994), three-quarters of cardiovascular disease may occur in "normotensive" individuals. It has been estimated that lowering DBP by 2 mm Hg in the population as a whole may be as effective in reducing the rate of CHD than treating individuals with DBP above 95 mm Hg (Cook et al. 1995). Reduction of blood pressure in the population as a whole may be the key in reducing the number of cardiovascular events.

In analysis of published studies of the effect of differences in diastolic blood pressure on the risk of heart disease and stroke (MacMahon et al. 1990), no threshold for level of blood pressure was determined. For an average 5-6 mm Hg difference in diastolic blood pressure, a steeper increase in the risk of stroke was found, compared to increase in

the risk of heart disease. A difference of this magnitude (5-6 mm Hg) could account for avoidance of one third the risk of stroke and one fifth the risk of heart disease. High blood pressure has been universally reported as the number one risk factor for stroke (Lassen 1996). Isolated systolic hypertension defined by high levels of systolic blood pressure with normal levels of diastolic blood pressure has been shown to be a powerful risk factor for stroke in the elderly (Menard et al. 1992). There is a strong association of SBP with both IHD and stroke in men at younger ages, while DBP is more important as a risk factor for IHD at older ages, SBP remains the more powerful predictor for stroke (Rabkin et al. 1978a). Further, increases in SBP in young men (Rabkin et al. 1978b) have been shown to predict stroke, and also changes increases in SBP just before stroke have been associated with a poor prognosis (Rabkin et al. 1978a). The Framingham Study has reported SBP, rather than DBP, to be a more powerful predictor of CHD (Kannel et al. 1970). Increased variance of repeated SBP measurements has recently been examined in relation to CHD (Grove et al. 1997) and shown to be positively associated with increased risk.

There is a positive gradient with blood pressure and incidence of CHD, but the association has been described as more "J-shaped" post myocardial infarction for re-infarction (D'Agostino et al. 1991, MacMahon 1991). A "U" shaped relationship between DBP and cardiovascular mortality following myocardial infarction, has led to speculation that low blood pressure and low blood flow may accompany those with severe heart disease (D'Agostino et al. 1991).

3.4.2 Treatment of high blood pressure

Because high blood pressure is a major risk factor for cardiovascular disease, efforts have been made to evaluate the impact of lowering blood pressure. A recent meta analysis of 14 randomized control trials examined evidence for the effect of pharmaceutical treatment of high blood pressure involving a total of 37,000 individuals, where it was concluded that the largest effect of reducing blood pressure on cardiovascular disease was with the reduction of stroke (Collins et al. 1990a, Collins et al. 1990b). Reduction of DBP by 5 to 6 mm Hg over 5 years on the average resulted in an overall 45% decrease in the rate of fatal stroke and 42% in overall strokes. In contrast, rates of fatal and all (fatal and non-fatal) cardiovascular disease were reduced by 11% and 14%, respectively. Overall, there was a reduction by 21% in all cardiovascular (including stroke) deaths, and no difference in deaths due to non-vascular causes.

The treatment of isolated systolic hypertension, (SHEP Cooperative Research Group 1991) has reported relative risk of 0.75 and 0.74 for stroke and heart disease, with no difference in total mortality reduction after five years. Risk factor profile scores for stroke developed from Framingham data in 1991 (Wolf et al. 1991a), have been revised (D'Agostino et al. 1994) to reflect antihypertensive treatment.

3.4.3 High blood cholesterol

Elevated blood cholesterol is a major risk factor for cardiovascular disease, with the four components: plasma cholesterol, triglyceride, LDL and HDL have varying strengths of association with cardiovascular disease. Increasing values of total

cholesterol and increasing values of LDL cholesterol are both positively associated with increasing risk of CHD. Increasing values of HDL cholesterol are associated with a lower risk of atherosclerosis and cardiovascular disease. The importance of high HDL values as a protective factor for CHD has been reported to be independent of levels of total cholesterol and perhaps of stronger value in women than in men (Neil HAW et al. 1990). A stronger association with steeper gradients of risk was shown when both elevated total cholesterol and low HDL cholesterol are considered together. Dr. Castelli, current medical director of the Framingham Study, stressed this in his address at the 1995 Canadian Cardiovascular Society's Annual Meeting based on a Framingham report (Castelli et al. 1986) showing the joint effect of the two lipid measures on incidence of heart disease. With both components being important predictors, a strong relationship has been found with the ratios of LDL/HDL or total cholesterol/HDL to cardiovascular disease. The triglyceride component appears to have a positive, but somewhat weaker, association with cardiovascular disease, than do LDL and HDL (Miller 1999). The predictive value of total cholesterol decreases with advancing age while the ratio values continue to be associated with cardiovascular disease at older ages.

Numerous trials have shown that elevated blood cholesterol levels can be reduced through the use of pharmaceuticals and in turn that reduced total and LDL cholesterol levels have resulted in a reduction of total and cardiovascular mortality. A recent meta-analysis suggested that a 10 percent reduction in cholesterol could translate into a 20 to 25 percent reduction in IHD morbidity (Law et al. 1994). Pharmacological treatment has

been shown to reduce the risks of both stroke and CHD mortality (The LIPID Study Group 1998).

Diet is central to the role of cholesterol in the development of cardiovascular disease. Early animal studies and observational studies of native populations lead to the association between high rates of cardiovascular and "rich diets". "Rich diet" has been described (Stamler 1995) as: "habitual fare high in animal products and processed animal products, high in total fat, hydrogenated fat, and separated (visible) fat, high in cholesterol and saturated fat, high in refined and processed sugars, high in salt, high in alcohol for many in the population, high in caloric density, in 'empty' calories, and in ratio of calories to essential nutrients, low in potassium, fiber and often other essential nutrients, and high in total calories for a low level of energy expenditure in the era of the automobile, television and mechanized work." This diet produces above optimal levels of serum cholesterol, blood pressure and body weight, beginning in childhood. Dietary cholesterol intake, is fortunately one factors an individual can exercise control, however, modification of high dietary cholesterol has been shown to have only moderate impacts on blood cholesterol (Hegsted et al. 1993).

3.4.4 Smoking

It was stated in the 1964 US Surgeon General report: "It is also more prudent to assume that the established association between cigarette smoking and coronary heart disease has causative meaning than to suspend judgment until no uncertainty remains." (Surgeon General Report 1964). The 1983 US Surgeon General's report on smoking and

cardiovascular disease concluded that due to its prevalence "cigarette smoking should be considered the most important of the known modifiable risk factors for coronary heart disease in the United States" (Surgeon General Report 1983). The 1983 report identified smoking as a major cause of cardiovascular disease for men and women, with smokers having a 70% greater cardiovascular death rate than non smokers. Smokers have a 2 fold increased incidence of IHD and heavy smokers a 4 fold increased risk above non-smokers. These risk ratios are of similar magnitude for men and women.

Smoking rates have been declining from a high of three-quarters of adults at the end of WWII, to 29% of the Canadian population smoking in 1992 (Stachenko et al. 1992). Smoking is a powerful risk factor for cardiovascular disease at every level of other factors, but is perhaps operating through a mechanism other than the promotion of atherosclerosis (Surgeon General Report 1983). While the specific mechanisms through which smoking may operate with cardiovascular disease is not certain, smoking has been shown to have a deleterious effect on endothelial functioning. Also, it is thought that as nicotine from tobacco stimulates the heart, an increased heart rate may produce a temporary rise in blood pressure. Further, the carbon monoxide levels of inhaled cigarette smoke consequently decrease the available supply of oxygen to the heart.

Smoking incurs an increased risk of IHD for men, primarily through manifestation of myocardial infarction and sudden death (Tate et al. 1997b). Smoking is a more powerful risk factor in men than in women (Dawber 1980). In the British doctors'

Study (Doll et al. 1994), the relative risk for smoking and mortality was reported to be 1.6 for ischemic heart disease and 1.3 for stroke.

While smoking may be a potent risk factor for cardiovascular disease, it is also one factor that the individual has almost exclusive personal control over. While the adverse effects of smoking are far-reaching (Wald and Hackshaw 1996), the benefits of quitting smoking have been shown to be immediate, and substantial, regardless of how long a person has smoked (Kannel and Schatzkin 1983).

The Oslo Study Group reported a 47% reduction of CHD in an intervention group targetted with changes in both diet and smoking cessation as compared to a control group (Hjermann et al. 1981).

Non-smoking individuals exposed to environmental tobacco smoke, i.e. "second-hand smoke", have been shown to have a greater progression of atherosclerosis over a 3-year period as measured by increase in the intimal-medial thickness of the carotid artery (Howard 1998).

3.4.5 Diabetes Mellitus

Diabetes mellitus is a disease associated with the body's inability to control its blood glucose levels. This can result from impaired insulin production or the body's inability to use insulin properly. This disease can be controlled to some extent through pharmaceutical intervention and diet (Report of a WHO Study Group 1994).

"Coronary artery disease by any measure is more common in diabetics than non-diabetics leaving the diabetic from two to four times as likely to die from myocardial

infarction or heart failure as the non-diabetic" (Sniderman et al. 1992). Diabetic men and women have been shown to have two to three fold increased risks of cardiovascular disease respectively at any levels of the major risk factors (United States Department of Health Diabetes Surveillance 1990). A feature of diabetes as a risk factor for IHD is its differential effect in men and women, where risk ratios for IHD in women are double those for men. In the Framingham study risk ratios of 2.4 for men and 5.1 for women (Kannel 1985) and in the Rancho Bernardo study risk ratios of 1.8 and 3.3 respectively (Barrett-Connor et al. 1991) were reported. Insulin dependent diabetes is more strongly related to cardiovascular disease than non-insulin dependent diabetes. Diabetes is associated with many cardiovascular risk factors, including high blood pressure, cholesterol levels and obesity. It may be that it is through these factors that the effect of diabetes on CHD is most apparent. However, diabetes remains an independent factor in most multivariate analyses of cardiovascular disease (Kannel and McGee 1979, Rosengren et al. 1989, Ford and DeStefano 1991). Multivariate risk ratios for diabetes and stroke range from 2.1 to 3.2 reported by the Cardiovascular Health Study (Manolio et al. 1996). Risk ratios for diabetes have also been reported to be greater for stroke outcomes than for heart disease outcomes (Ruderman and Haudenchild 1984).

3.4.6 Body build, overweight and obesity

It is generally agreed that obesity as a measure of excess body fat is associated with adverse health outcomes and increased total mortality. The epidemiology of obesity has been reported in extensive detail (Black et al. 1983). The proportion of Canadian

adults with body mass index above 27 kg/m^2 was reported to be 35% of men and 27% of women (Reeder et al. 1992). There has not been general agreement, however, about the role of obesity as an independent cardiovascular risk factor. Other functions of height, weight and body build including body mass index, skin fold and relative body weight have been associated with cardiovascular mortality and less so cardiovascular morbidity (Keys et al. 1972), when adjusted for other risk factors. Relative weight, weight divided by height, has been used as a measure of build, and found to be significant in men for heart disease and in women for stroke, as reported by the Framingham study (Hubert et al. 1983). The Framingham Study has also reported a somewhat "J" shaped relationship with cardiovascular outcomes (Sorlie et al. 1980). The Nurses Study of females, reported that body mass index was an important factor for cardiovascular disease, but that waist to hip ratio was a stronger predictor (Manson et al. 1995). Waist hip ratios have been used in some populations, and more recently interest has focused on measures of central adiposity suggesting that the distribution rather than the mass of body fat may be the important factor in assessment of cardiovascular risk (Lenfant 1997). It was shown that waist circumference was highly correlated with SBP, DBP, HDL cholesterol and triglycerides but not with total or LDL cholesterol (Reeder 1997).

Obesity is associated with high blood pressure, high cholesterol, diabetes and sedentary lifestyles. It may be that the influence of obesity on cardiovascular disease operates through association with these factors, and favourable effects on reduction of levels of these factors has been shown to coincide with weight loss. Both increases and

decreases in weight have been reported to be associated with an increased risk of CHD (Walker et al. 1995), while stable weight from age 50 through 65 years was associated with better cardiovascular health, than either weight gains or weight losses (Harris 1997). Fluctuation in body weight has been shown to have negative cardiovascular health outcomes (Lissner 1991). Height alone, has been reported to be predictive of CHD (Krahn et al. 1994, Hebert et al. 1993) but not for stroke (Hebert et al. 1993).

3.4.7 Age and gender

There is an increasing incidence of cardiovascular morbidity with age for both men and women. The age-specific incidence of ischemic heart disease is greater for men than for women, while the incidence of cerebrovascular disease is similar in males and females (Heart and Stroke Foundation of Canada 1999). Mortality rates of cardiovascular disease in men are double those of women, for all manifestations other than stroke. Pre-menopausal women with normal estrogen levels are virtually free of cardiovascular disease, at older ages the rates of disease become more similar for men and women.

3.4.8 Other risk factors

An individual with a positive family history of CHD is at increased risk of CHD (Hamby 1981). Further, increased levels of cardiovascular risk factors are found in individuals with a positive family history of cardiovascular disease (Barrett-Connor and Khaw 1984). Some evidence for family history of stroke exists, where men whose mothers died from stroke were at a three-fold increased for stroke, but no increased risk was inferred if fathers had died from stroke (Welin et al. 1987). It may be through the

increased familial risk of hypertension and diabetes that those with a positive family history of either CVD are at increased risk themselves. Further a genetic component may influence risk of cardiovascular disease through inherited characteristics such as height or stature.

Newly emerging biological risk factors for CHD are being investigated. Elevated levels of an ameno acid, homocysteine, have been shown to damage the endothelial wall and be associated with increased CVD mortality (Nygard et al. 1997). Haemostatic factors, including fibrinogen, may be strongly linked to smoking, and has been shown to is a risk factor for CVD (Stone and Thorp 1985, Kannel et al. 1987).

Recently the association between socioeconomic status (SES) and cardiovascular disease was reviewed (Kaplan and Keil 1993) wherein, a similar association to that observed between SES and general health has been reported. Lower SES was associated with higher rates of cardiovascular morbidity and mortality. Risk factors for coronary heart disease, i.e. blood pressure, smoking rates, and body mass index, are all higher in men and women with the lowest income or lowest education levels (Luepker et al. 1993). The INCLEN Multicentre collaborative study (INCLEN Research Group 1994) has reported highest risk factor levels in regions and countries with lowest extent of socio-economic development. Blood pressure and body mass index have been found to be higher in men with lower-status occupations (Opit et al. 1984). SES indicators, including occupation, have been shown to be associated with early carotid atherosclerosis (Lynch et al. 1995). An analysis of the data from nearly 2,000 males interviewed in the 1978

Canadian Health Survey found overall weak but not significant relationships between occupations and health, but the "manual labourer" group did have a consistent trend towards poorer health (Hay 1988). After adjustment for other risk factors, SES indicators including occupation have been shown by some to remain statistically associated with coronary heart disease (Woodward et al. 1992).

The British studies of civil servants, (Marmott et al. 1978, Rose 1981) show strong relationships of social class and heart disease mortality, independent of other risk factors. In Sweden, the Karasek model (Karasek et al. 1981) has explored job control on risk of heart disease and stroke. Low control, high demand occupational situations were shown to be associated with a high risk for heart disease and stroke. It was further reported that men with low work control, or low work control and low social support had relative risks of 1.83 and 2.62 respectively for cardiovascular mortality (Johnson et al. 1996).

Left ventricular hypertrophy (LVH) is a strong predictor for CVD and stroke. Aside from age and obesity, hypertension is a main determinant of LVH (Kannel 1991). Further, it has been reported that control of hypertension, has resulted in a decline in LVH (Mosterd 1999). LVH was reported to be "one of the less common but ominous risk factors for coronary disease, stroke and cardiac failure" (Kannel 1991). Atrial fibrillation is a strong predictor of both stroke morbidity, stroke mortality and heart disease mortality (Krahn et al. 1995) where in the Manitoba Follow-up Study multivariate risk ratios of 2.07, 2.48 and 1.41 were reported, respectively. Relative risk for stroke

were reported to be greatest in the elderly male with relative risks 3 to 4 fold (Wolf et al. 1991b). Evidence associated with major electrocardiographic abnormalities, including Q waves, left axis deviation, T-wave inversion, left bundle branch block and rhythm disturbances have been reviewed in men (Sox et al. 1989) and been reported to have increased risks of heart disease mortality and higher risks of heart disease and cardiovascular mortality (Cedres et al. 1982).

Leisure time physical activity has been examined separately from physical activity "on the job" for risk of heart disease (Salonen et al. 1988). Adjusted for other risk factors, physical inactivity in leisure time was associated with a significant odds ratio of 1.2, whereas it was 1.3 for sedentary occupations. For CHD, the Framingham Study reported a "clear trend" of favourable outcome with increasing level of physical activity for all ages, including the elderly (Kannel et al. 1986a).

Some perhaps more curious risk factors have included a report that men may be more likely to suffer cardiovascular events on Monday compared to other day of the week (Rabkin et al. 1980), that risk of myocardial infarction increases with degree of baldness (Lesko et al. 1993, Wilson and Kannel 1993) and that snorers have an increased risk of stroke in the 30 minute period immediately following waking (Palomaki et al. 1989). Some of these prompted a title in Time Magazine, "What's a short, bald-headed, pot-bellied guy to do?" (Lemonick 1993).

3.4.9 Combinations of risk factors

It has been said that cardiovascular disease is a multifactorial disease. Risk factors for cardiovascular disease tend to be highly correlated. Blood pressure tends to increase with age, as does cholesterol with age. Smokers have been shown to have higher blood pressures than non smokers, and in general, males have higher blood pressures than females. Cardiovascular mortality was greatest in the obese, had a linear increasing relationship with BMI in non smokers and a somewhat "U-shaped" relationship with BMI among smokers (Wannamethee and Shaper 1989). Diabetics tend to have higher risk factor levels, although the effect of diabetes remains independent in most analyses of risk (Kannel 1979, Kannel 1985). Many epidemiological models of risk factors and cardiovascular disease have repeatedly shown the statistical independence of most cardiovascular risk factors. Hence, the importance for understanding the multifactorial nature of cardiovascular disease and these implications are that risk of cardiovascular disease will increase rapidly with evidence of each risk factor. For example, in men, the risk of ischemic heart disease doubles as total cholesterol increases from 5.2 to 6.2 mmol/l, with elevated blood pressure it doubles again, and for a smoker, double again (Stamler et al. 1986). Thus, a man with all of these risk factors would be at a risk of IHD eight times greater than a man without any of the three.

It has been estimated from the Framingham data that individual level risk factors, i.e. high blood pressure, obesity, elevated serum cholesterol, smoking, diabetes and a sedentary lifestyle, account for about fifty percent of cases of coronary heart disease

(Kuller 1976). However, many other unknown risk factors must also contribute to the incidence of CHD. The relative importance of cardiovascular risk factors was estimated (Kaplan and Stamler 1983, Stamler et al. 1993b) using standardized logistic regression coefficients. For both men and women, age 45 through 74 years, over a 20 year follow-up period, hypertension was the strongest positive factor, followed by serum cholesterol, electrocardiographic evidence of left ventricular hypertrophy and cigarette smoking. These factors had varying levels of risk when examined for differing manifestations of disease.

3.5 Contributions of the Manitoba Follow-up Study to knowledge of the epidemiology of cardiovascular disease

To date, thirty-nine papers have been published based on the findings of the MFUS. Many hypotheses concerning the relationship between blood pressure and body build to development of ischemic heart disease and stroke have been examined. Patterns of these risk factors over time have been described, and some effects of aging on these risk factors have been reported. Some of these publications and their findings, pertinent to the objectives of this thesis, will be described.

3.5.1 Blood pressure, body build and cardiovascular disease in the Manitoba Follow-up Study

After 15 years of follow-up, to 1963, (Mathewson et al. 1965b) the first paper describing build and blood pressure with the development of coronary heart disease was published. During this follow-up interval, 210 men had died and 143 had developed

coronary heart disease. Fifteen percent of subjects were classified as hypertensive on the basis of having had at least one SBP reading above 159 mm Hg or at least one DBP reading above 94 mm Hg. Within "normal", "borderline" and "hypertensive" categories, there was an increasing risk of development of coronary heart disease. The rate of coronary heart disease was 1.77 times greater in hypertensives than in the cohort as a whole. Subjects were classified as "under weight", "normal weight" and "over weight" on the basis of their body weight at entry to the study and again based on their body weight recorded fifteen years later. Within the nine combinations of weight at entry and weight fifteen years later, there was no variation in coronary heart disease rates, however, the "over weight" group was "too small to permit a reliable statement".

After 26 years of follow-up, to 1974, 390 subjects had developed evidence of ischemic heart disease and 78 subjects cerebrovascular disease. While it was well recognized that increased blood pressure was related to both of these events, the relative value of SBP versus DBP for the prediction of these diseases was less certain. An analysis of the two BP measurements at entry and at four points in time during the study revealed that when both blood pressures were considered together in the same multiple logistic regression model, or each blood pressure, SBP or DBP, were entered in separate models, a stronger association with cerebrovascular disease was found for systolic compared to diastolic blood pressure at entry and at most of the other examinations. For IHD, diastolic blood pressure showed a stronger association at the earlier examinations, whereas systolic pressure was more important when the majority of the cohort was

between 40 and 50 years if age (Rabkin et al. 1978a). Little attention had been given to the analysis of change in risk factors for cardiovascular disease. With 26 years of longitudinal data, changes in blood pressure were analyzed in relation to cerebrovascular disease (Rabkin et al. 1978c) and ischemic heart disease (Rabkin et al. 1979). It was found that after adjusting for age and SBP at entry using the logistic regression model, change in SBP was significantly associated with an increased risk of subsequent cerebrovascular disease. Changes over previous five year intervals were more important than changes over longer intervals. Similarly, repeated measurements of SBP and changes in SBP were related to subsequent development of IHD. "After adjusting for entry age and SBP, change in SBP from entry to the later four examinations showed a greater increase in those over 45 years of age, for longer intervals between measurements and most importantly in those who later developed IHD. In multivariate analysis, SBP after entry was more strongly associated with IHD incidence than entry SBP." (Rabkin et al. 1979).

Body weight and its relationship with ischemic heart disease was analyzed using the 26 year follow-up data. The role of overweight for ischemic heart disease was unclear, some studies had shown weight to be independently associated with ischemic heart disease (Kannel 1967) while others had not (Keys 1972). The relationship of BMI in younger and older men (under and over age 40 years), for short, medium and longer term follow-up (first 16 years, next 5 years, and last 5 years) was examined for each manifestation of ischemic heart disease (Rabkin et al. 1977). The effect of BMI for

younger men was only evident after 16 years of follow-up. While associated with all manifestations of ischemic heart disease, high body mass index was most strongly associated with myocardial infarction and especially sudden death. Analysis of another feature of body build, height, showed that height was not correlated with blood pressure and body mass index, and that height was inversely related to ischemic heart disease morbidity, cardiovascular mortality and total mortality (Krahn et al. 1994).

3.5.2 Patterns of blood pressure and body build tracking in the Manitoba Follow-up Study

In 1972, a detailed report of blood pressure patterns over the first 20 year of the study was published (Mathewson et al. 1972). Three patterns describing the transition over time from normotensive levels to hypertensive blood pressure values were observed. With SBP over 140 mm Hg or DBP over 90 mm Hg used as a cut point for defining elevated BP, one pattern has "blood pressure fluctuating above and below 140/90 over the whole period of observation"; a second pattern had "increases in pressure, both systolic and diastolic, occurring in plateau. At the beginning, this pattern is indistinguishable from the first pattern"; and the third pattern, "following a 15-year period of intermittent elevations resembling the first pattern, the blood pressure abruptly increased to high levels within a period of a few years." A fourth pattern included those whose BP readings over the first 20 years always were observed below 140/90 mm Hg. It was concluded that "at the exposed ages each entry level of blood pressure, both systolic and diastolic, was related significantly to subsequent blood pressure behavior." Patterns of

body build and blood pressure over time were re-examined after 27 years of follow-up in 3054 subjects who had remained alive and free of IHD and or stroke (Hsu et al. 1977). It was concluded that "BMI, SBP and DBP tend to retain their relative positions in their own distributions even after 25 years." Correlation between initial and later measurements remained significant, although decreasing in magnitude and correlation of measurements five years apart were greater in older men than in younger men.

Tracking of blood pressure was examined after a 30 year observation period to determine the relationship of initial BP to subsequent BP in the subcohort of younger men age 20 through 39 years of age at entry (Rabkin et al. 1982). Correlation coefficients for repeat SBP and DBP measurements within 5-year age categories at entry were calculated for repeat measurements at five year intervals and found to increase with advancing age and decrease with increasing interval of time between measurements. Subjects whose BP was more than 1 standard deviation unit above the mean at entry were more likely than others to have BP more than 1 standard deviation unit above the mean at later measurement. Similarly, those subjects whose BP was less than 1 standard deviation unit below the mean at entry were more likely to have BP less than 1 standard deviation unit below the mean at later measurement. This finding held up to 20 years after entry to the study. It was concluded that "BP in later life can be predicted from BP at ages 20-39 years and can identify groups at high or low risk for hypertension."

This theme was expanded with a re-examination of evidence for tracking for SBP and DBP, based on all subjects after 40 years of follow-up (Tate et al. 1995b). Two

methodological approaches, correlation of repeat measurements and a calculation of the relative likelihood of remaining in the top or bottom quintile of the BP distribution at subsequent measurement confirmed significant BP tracking. BP tracking was strongest for middle age men, 45 to 55 years of age and decreased with increasing interval of time between measurements. This analysis provided further evidence that young men at highest risk of hypertension in later life can be identified, and hence "strategies for prevention of cardiovascular complications can be targeted in early adulthood".

3.5.3 Aging and risk factors in the Manitoba Follow-up Study

While there is little doubt that BP, smoking and BMI are predictors of long term coronary heart disease morbidity and mortality, an analysis over 45 years of follow-up examined whether the effects of these risk factors on manifestation of ischemic heart disease were modified with aging (Tate et al. 1998). It was shown that the effects of SBP, DBP and smoking declined with age to the point that after age 65 years, these three risk factors were no longer significantly associated with ischemic heart disease incidence. The effects of diabetes mellitus and BMI did not significantly change with age. It was concluded that "This dynamic relationship must be kept in mind when planning strategies for prevention of cardiovascular disease."

3.6 Other longitudinal studies of cardiovascular disease

The objectives of this thesis relate to the epidemiology of cardiovascular disease morbidity. Specifically, the incidence of IHD and its manifestations over time and effect

of aging on the distribution of risk factors for IHD will be examined. Evidence for tracking of blood pressure and BMI will be explored. As well, the potential for tracking as an additional risk factor for IHD will be assessed. These objectives are important to the understanding of risk factors, aging and IHD, but are possible to analyze only with longitudinal data. Hence, the MFUS is well suited to address these hypotheses. Other longitudinal studies have been undertaken around the world with different cohorts for similar purposes. Some aspects of these studies will be described in the following sections.

3.6.1 The Chicago Cohorts

The long term impact of cardiovascular risk factors on total and cardiovascular mortality is being investigated using the combined data of three studies under taken during the 1950s in Chicago and followed since then. The studies are as follows: The Western Electric Company cohort of 1,903 men aged 40-55 years from the fall of 1957, 1,594 men employed by the Peoples Gas Company age 40-59 years from January 1958 and 1,609 male employees from this company age 25-39 in January 1959 (Stamler et al. 1993b). For some analyses these cohorts have also been merged with other cohorts from the Chicago Heart Association Detection Project in Industry.

3.6.2 The Pooling Project

By the early 1960s a number of longitudinal studies aimed at CHD were underway in the US. In 1964, the data from the men of five studies were pooled. These five included data from the Albany civil servant study, Chicago People's Gas Company,

Chicago Western Electric Company, and the Framingham and Tecumseh studies (The Pooling Project 1978). Over the next few years, data from an additional eight studies were involved. In 1978, the final report of this project was published, presenting distributions of risk factor profiles, and CHD incidence based on close to 100,000 person years of observation from 12,516 men age 40 to 64 years.

3.6.3 The Framingham Study

Initiated in the same year as MFUS, the Framingham Heart Study has been following the lives of 5,127 residents of Framingham , Massachusetts with biannual examinations, primarily aimed at the detection of cardiovascular disease (Dawber 1980). The Framingham study continues today, and is recognized as the world's greatest contributor to the knowledge and understanding of the epidemiology of cardiovascular disease.

3.6.4 Honolulu Heart Study

The Honolulu Heart Program is a prospective epidemiologic investigation of coronary heart disease and stroke among men of Japanese origin who were born in the years 1900-1919 and living on Oahu in 1965 (Benfante et al. 1989). At baseline screening, 5919 men age 46 through 59 years were free of CHD and stroke and were subsequently followed for development of new CHD.

3.6.5 The Rancho Bernardo Study

Between 1972 and 1974, 82% of the residents living in Ranch Bernardo, California between the ages of 40 and 79 years were enrolled in a population based study of CHD (Criqui et al. 1978). These 4014 men and women were followed for 9 years for development of CHD, providing contributions to the literature on differences in risk factor effects in men and women.

3.6.6 The Quebec Cardiovascular Study

A cohort of 4576 men aged 35 to 64 years living in seven communities around Quebec City, Canada, were enrolled in this study in 1974 (Dagenais et al. 1990a). Baseline risk factors for cardiovascular disease have been related to development of cardiovascular disease. Over a 12 year follow-up period to 1986, 603 first CHD events were documented.

3.6.7 Goettingen Risk, Incidence and Prevalence Study (GRIPS)

In order to estimate the "impact, ranking and potentiating power" of cardiovascular risk factors, a cohort study of 5790 men age 40-59 years were followed prospectively with a 97.4% response over 10 years to document morbidity and mortality (myocardial infarction, sudden death and CHD death) (Cremer et al. 1997).

3.6.8 The Gothenberg Study

At age 50 years, in 1963, 88% of eligible men, one third of all men born in Gothenburg, Sweden in 1913, were enrolled in a study. The baseline examination was

supplemented with a second exam in 1967, again in 1973 and 1980. Incidence of CHD and stroke was examined after 18.5 and 25 years (Welin et al. 1987, Welin et al. 1993).

3.6.9 The Copenhagen City Heart Study

A baseline exam of 14,233 residents was conducted in 1976 through 1978. The study was designed to "evaluate the incidence of and risk factors for cardiovascular disease" (Nyobe et al. 1989). An average follow-up of 6.5 years up to the end of 1983 provided data for estimation of incidence of CHD and evaluation of risk factor effects.

3.6.10 The Charleston Heart Study

A study population in Charleston, South Carolina of just over 2,000 black and white men and women age 35 years and older in 1960 were enrolled in this study. They were followed over the next 28 years with four recall examinations to determine the relationship of cholesterol measurements in these four subgroups to total and CHD mortality (Keil et al. 1992).

3.6.11 Alameda County Study

All male state workers in Albany, New York were invited to enter a prospective study to detect hypertension and CHD over time. Eighty-nine percent of eligible employees, 1910 men in total, were recruited during 1953 and 1954 (Hilleboe et al. 1954). Baseline and repeat measurements of cardiovascular risk factors have been obtained over a 30 year follow-up period and related to CHD morbidity and mortality.

3.6.12 The Bogalusa Study

The Bogalusa Heart Study was designed to track cardiovascular risk factors in children (Berenson et al. 1995). This study was designed to provide information on both males and females of different racial origins. A population of approximately 5,000 children has been followed since 1974 with repeat examinations. The study aimed primarily at providing information on distribution and prevalence of risk factor values in a pediatric population, whether risk factors track in young populations, and the interrelationship of coexisting risk factors in the young.

3.6.13 The Muscatine Study

A study designed to examine tracking of blood pressure in children was undertaken in Muscatine, Iowa where a cohort of 4313 children age 5 through 14 years of age were enrolled in 1970 (Clarke et al. 1978). Three to six measurements of blood pressure in these children over a period from four to ten years provided data to examine BP patterns inherent in individuals with repeat measurements over time.

3.6.14 The Amsterdam Growth and Health Study

Longitudinal data involving five repeat measurements of blood pressure over a 9 year follow-up period of 200 adolescents from ages 13 through 21 years were collected to address questions of tracking of values from teenage years to adulthood (Kemper 1990).

3.6.15 Normative Aging Study

This longitudinal study of health and aging was established by the Veterans Administration in the US. Community residents from the Boston area were identified

and 2280 male volunteers age 21 to 80 years, were enrolled in 1963 (Cassano et al. 1990). The study is ongoing, with repeat examinations including BP measured at 5-year intervals before age 52 years, and every 3 years thereafter. The study is ongoing, and primary mortality endpoints are being recorded.

3.6.16 Cardiovascular Health Study

In 1990, an attempt was made to recruit 1250 residents, men and women, age 65 years and older from each of four communities across the US to form the 5000 member cohort of the Cardiovascular Health Study. Baseline and repeated physical examinations were planned over time to address the following five objectives of this study: "1. To quantify associations of conventional and hypothesized risk factors with CHD and stroke. 2. To assess the associations of indicators of subclinical disease, identified by noninvasive measures such as carotid ultrasonography and echocardiography, with the incidence of CHD and stroke. 3. To quantify associations of conventional and hypothesized risk factors with subclinical disease. 4. To characterize the natural history of CHD and stroke, and identify factors associated with clinical course. 5. To describe the prevalence and distributions of risk factors, subclinical disease, and clinically diagnosed CHD and stroke" (Fried et al. 1991).

4 STUDY DESIGN, PROCEDURES AND METHODS

In general, epidemiological studies are investigative procedures designed to examine the association between exposure and disease. Longitudinal studies are characterized by an element of time. Specifically then, in an epidemiological longitudinal study of disease, the determination of exposures of individuals or the observation of disease development, or both, are determined at more than one point in time.

Epidemiology has many definitions, but most definitions include an investigation of some aspects of the frequency, distribution and determinants of disease in a population (Hennekins and Buring 1987). Longitudinal epidemiologic studies of CVD frequently focus on the morbidity and mortality of manifestations of CVD. An analysis may include the frequency or incidence of CVD within populations, or the distribution of CVD in subgroups of populations, of men and women, by age, or geographic region. The determinants of CVD may be investigated by examining the association of predisposing factors or characteristics of disease free individuals to the subsequent manifestation of CVD. Through the examination of healthy individuals before evidence of disease, during the manifestation of disease, and prognosis of individuals following disease onset a complete longitudinal investigation of CVD can be performed. Hence, longitudinal epidemiologic studies of CVD, may investigate the "natural history" of CVD.

4.1 Design options for longitudinal studies of cardiovascular disease

4.1.1 Classification of longitudinal research designs

Because the element of time is present in all longitudinal studies, the possibility exists for examining the relationship between characteristics (exposure) and outcome (disease) from two directions. The selection of the sample for study can be based on either the outcome or exposure of interest, or some other criteria. Further, the timing of a study describes the relationship, in calendar time, between the collection of data and the conduct of the study. Exposure and outcome for analysis may have both occurred prior to the conduct of the study or are determined concurrently with the conduct of the study, or some combination of these directions is possible. Studies of relationships from exposure forward in time to the development of disease are called cohort studies. Studies looking back in time examining the prior characteristics of diseased and non diseased individuals are called case-control studies.

The classification of epidemiologic studies based on these three considerations has been suggested in order to present a consistent definition of study designs using consistently defined terms (Kramer and Boivin 1987). Hence, the directionality of the study, selection of the sample and timing of the conduct of the study all determine the type of research design. The MFUS is an example of a cohort study (directionality), whose participants were recruited (selection) by convenience on the basis of a common experience, i.e. active participation in aviation, either the RCAF during WWII or

commercially in the late 1940s, with a determination of exposure and outcome conducted concurrently (timing) over time.

Both cohort and case-control studies involve an element of time and both have their relative merits and weaknesses. Cohort studies require following a group of individuals over a period of time to determine outcomes, and hence the commitment of both individuals and resources is necessary to conduct the study and collect the data before any analysis of the relationship with exposures of interest can be made (Liddell 1988). On the other hand, case-control studies may be quicker and cheaper to undertake, as both outcome and exposure data necessary for analysis have already occurred. However, all exposure data may not necessarily be available, nor complete, as completeness and accuracy of information about exposure will rely on existing records from the past. Further, in cohort studies there is no uncertainty about the temporal relationship between exposures and disease manifestation, as initially disease free individuals will be followed forward in time to onset of disease. The same is not true with case-control studies, where both the exposure and disease onset have already occurred when the time study is undertaken, and the temporal relation between the two may be uncertain. Because of these reasons, the study of CVD requiring risk factor information before the incident event is rarely feasible to undertake as a case-control study.

4.1.2 Population level versus individual level studies

Longitudinal studies may be undertaken for a variety of reasons (Kalton 1992). There may be interest in the determination at the aggregate or population level of the change of the burden of illness in a population over time. Change in the distribution of population characteristics or change in factors associated with disease may be important to adjust strategies for CVD prevention interventions. Aggregate changes over time in population characteristics or disease levels may be indicative of previous successful interventions. On the other hand, it may be that individual level changes are of interest. Individuals whose characteristics change over time may have a different outcome than the individuals whose characteristics remain stable.

In prospective, longitudinal studies, the same fixed group of individuals may be followed over time, often with repeat measurements of characteristics, until the endpoint(s) of interest are reached. Alternatively, a different sample of individuals can be selected at points in time and examined. The collection of data at the individual level, from the same individuals, will permit the analysis of the relationship to endpoints determined later in time between both baseline characteristics and changes in individual characteristics. This has a distinct advantage over the collection of data from different cross sections of the population at points in time, where exposure data at one point in time is not linked with the individual at another point in time. Thus, at the population level, changes in distributions of exposure levels and changes in burden of disease in a

population can be determined, but only ecological statements of the relationship between the two can be made.

4.1.3 Prospective cohort studies of cardiovascular disease

The word "cohort" is derived from the ancient Roman term, describing military units or groups of soldiers. In the context of epidemiologic studies, a cohort is any group of individuals sharing a common set of characteristics. A cohort may be a group of individuals who were born in the same period of time, or who live in the same community, or who all had a common experience at the beginning of a study. In the epidemiologic investigation of CHD, the Norwegian study of men born in Oslo in 1913, the Framingham Study where the residents of Framingham, Massachusetts have been followed with repeat medical examinations since 1948 and the Manitoba Follow-up Study where a cohort of air crew recruits from the RCAF during WWII have been followed for more than 50 years are all examples of prospective cohort studies. A common feature of these studies is that one group of individuals was assembled, i.e. the size of the cohort was fixed at entry to the study, and this same group was followed over time. For reasons of practicality, the thousands of subjects of the MFUS or Framingham study could not all be enrolled to the study on exactly the same day. However a date sealing the cohort, following which no new subjects are entered, defines the fixed membership of the cohort for duration of the study.

Other longitudinal designs may allow for cohorts to accrue over time. For example, survivors of myocardial infarction discharged from a hospital may enter a

cohort study where prognosis within different regimens of treatment may be compared. Here subjects are not entered to the study at one point in time, but rather, qualify for inclusion over time, as eligible subjects are discharged from hospital. The progression of CVD, or prognosis following an index CVD event may be most efficiently examined with a study of this design, referred to as an inception cohort study.

The strengths and weaknesses of the type of cohort are linked to the reasons for undertaking the study. The natural history of CVD might be best examined with an initially disease free, fixed size, cohort followed over time. Longitudinal cohort studies, where the size of the cohort is fixed at the beginning of the study and the course of events experienced by this cohort of individuals is documented over time is called a follow-up study. Because this type of study requires following a cohort forward in time, it is often referred to as a prospective cohort study, or prospective follow-up study.

When a cohort study is being designed to examine the relationship of individual characteristics or exposure states to the subsequent development of CVD, the issue of who to include in this study is related specifically to who is available to be invited, who is at risk of disease, and what some of the expectations of development of disease would be in this cohort. For example, the incidence of CVD is greater in men than in women, increasing with age and greater in some geographic areas than others. A requirement for the validity of a cohort study is to obtain complete and accurate information on all members of the cohort. Cohorts comprised of individuals from a single workplace or organization may be easier to follow than a sample of individuals from a larger

population. One early example was that of the cohort of British physicians, assembled to examine the relationship between tobacco and cancer (Doll et al. 1994). A more recent example is that of a cohort of 121,700 female nurses who have been followed for over 20 years with questionnaires on lifestyle practices (Colditz et al. 1997). These cohort choices proved to be powerful designs as these studies were comprised of subjects who were easy to follow and motivated as to the study objective.

At the beginning of a cohort study of CVD the baseline examination will include an initial screening as only those free of CVD and hence at risk of development of CVD will be eligible for inclusion in the cohort. Exposure variables of interest to the study hypotheses need to be measured. As well, demographic characteristics of the cohort such as gender and age and perhaps current comorbid conditions are generally documented at entry to the study.

Critical to the choice of variables to measure in a study is the consideration to collect information on factors that might effect the relationship between the exposure and outcome being studied. A factor that is both related to the exposure being studied, but not a consequence of the exposure, and related to the outcome to be determined might influence the association between exposure and outcome. This phenomenon is referred to as confounding, and the factor in question is called a confounding variable. For example, in examination of the relationship between hypertension (the exposure variable) and CVD (the outcome), it is known that hypertension becomes more common with advancing age, and CVD is also more common at older ages. Care must be taken to control for age in

any examination of the relationship between hypertension and CVD so that an association found between hypertension and CVD can not be attributed to differences in age between hypertensive and non-hypertensive subjects.

Some studies, such as the Framingham Study and the Manitoba Follow-up Study, have included periodic physical examination in their designs to monitor risk factor profiles and determine disease status. Annual contact with all study members has been attempted to monitor vital status and maintain an "up-to-date" registry of addresses of cohort members. This has proven invaluable, both for minimization of subjects lost during the follow-up period as well as to ensure accurate documentation and timely recording of events.

The specific endpoints of interest need to be identified and clear definitions specified before the study begins. Depending on the duration of a study, flexibility of procedures for collection and coding should be considered to allow for changes in evolving diagnostic methods and disease coding conventions. A standard coding system already in use in other studies of similar design may be preferable to the development of a new system. This will enhance the possibility of comparisons between studies. Furthermore, the use of established valid and reliable instruments to measure characteristics is preferable.

A goal of the follow-up process is to obtain as complete and accurate information as possible about each subject's health outcomes. Outcome data may be collected over time as events occur or are determined at a point in the future from medical records and

vital statistics. The cost associated with surveillance of a cohort with routine medical examination or screening for new disease is greater than determination of outcome events at one point in time at the end of the study, but the accuracy and timeliness of the former method is greater. For documentation of mortality, vital statistics records may suffice to determine a subject's status at the end of follow-up. This will only be possible if careful records have been maintained to keep unique identifiers for the linkage to these sources.

The decision as to how long a study should continue and how frequently participants should be examined is a function of the specific research questions being addressed. To examine the association of risk factors measured in young adults with subsequent manifestation of CVD, a long follow-up interval, spanning decades will be required to accrue enough endpoints to have reasonable statistical power to test an association between the two. The frequency of re-examination of study participants will depend on whether changes in risk factors are expected to occur, and how frequent examinations of the cohort are necessary to document outcomes. Because of the long time spanned by many cohort studies of disease it is crucial to have the necessary commitment of personnel and finances to support the study to its projected completion. An investigation of incident CVD may span many decades before completion of the study.

4.2 Design of the Manitoba Follow-up Study

The Manitoba Follow-up Study is a prospective cohort study of cardiovascular disease. A cohort of 3,983 men was sealed on July 1, 1948. This cohort has been followed with medical examinations at regular intervals to determine risk factor profiles and document evidence of IHD. At the present time, this study is in its fifty-first year. Data used in the analyses undertaken for this thesis cover the 45–year follow-up period to July 1, 1993.

4.2.1 Contact procedures and examination requests

Procedures for collection of data including annual contact, medical examination requests and periodic questionnaires were described previously in Chapter 2. To summarise, annual contact by mail was used to monitor vital status and maintain an address registry. Medical examinations were requested every five years until 1965, and every three years since then and administered by each study member's personal physician or the medical staff of the Department of Transport. Examinations included a resting 12 lead electrocardiogram and measurement of SBP, DBP and body weight in addition to a general cardiovascular assessment. Since 1978, a one page questionnaire has been included with the annual contact letter. This questionnaire asks about physician contacts or hospitalisations occurring between examination requests, to enable timely follow-up and documentation of new medical information. Details of reported physician contacts or hospitalisations from the annual questionnaire were verified by correspondence with attending physicians and hospitals. Electrocardiograms and medical reports were

interpreted and coded independently by two physicians. Diagnoses of cardiovascular and non-cardiovascular comorbid events were recorded.

4.2.2 Definition of manifestations of ischemic heart disease

The onset of ischemic heart disease was defined by the date of the earliest manifestation of myocardial infarction, angina pectoris, or sudden death. The diagnostic criteria for these three events are as follows.

4.2.2.1 Angina Pectoris

Angina pectoris was identified by one of several manifestations. Typical stable angina was defined as chest pain of cardiac origin precipitated by effort, emotion or exposure to cold and relieved by rest or nitro-glycerine or both. Variant angina was defined by episodes of cardiac pain at rest or on recumbency in association with elevated ST segments. Unstable angina was defined by episodes of chest pain of cardiac origin, lasting approximately 30 minutes, associated with significant ST-T changes without enzyme elevations or abnormal Q waves; or chest pain typical of cardiac pain, associated with either elevated serum enzyme levels of twice normal or development of non-specific electrocardiographic findings including ST-segment or T-wave changes or ventricular conduction defects. Patients with positive exercise tests (horizontal or downward sloping ST depression of at least 1 mm) with chest pain were also included in this definition.

4.2.2.2 Myocardial Infarction

Myocardial infarction was diagnosed based on fulfilment of any of the following three criteria: 1) Classical acute myocardial infarction including clinical symptoms plus

elevated serum enzyme levels and new non specific electrocardiographic findings of ST-segment or T-wave changes or ventricular conduction defects; 2) Non-Q myocardial infarction defined as clinical symptoms consistent with myocardial infarction without development of new abnormal Q waves with or without elevated serum enzyme levels; and 3) Silent myocardial infarction defined by development of new abnormal Q waves without clinical symptoms.

4.2.2.3 Sudden Death

Based on the World Health Organization's definition, sudden death was defined as natural or non-violent death occurring immediately or within an estimated period of 24 hours after the onset of acute objective or subjective symptoms of ischemic heart disease (WHO Scientific Group). The cause of death for all sudden deaths is listed as due to ischemic heart disease.

4.2.3 Definition of risk factors

Five risk factors: SBP, DBP, BMI, DM and smoking were examined in this thesis. No blood lipid measurements have been recorded in this study. Age at examination was calculated to the nearest day using the difference between date of examination and date of birth.

Resting blood pressure, systolic and diastolic were obtained on routine medical examination and were recorded as reported by each subject's physician. No specific directions were given to physicians regarding protocol for measuring blood pressure or

body weight. If two or more measurements of blood pressure were reported at the same examination date, the repeat measurements were averaged.

Although body weight and blood pressure were requested to be measured on all physical examinations, body weight was not reported on some occasions. Body weight was more frequently not recorded on examination in the later years of the study. The height measurement, recorded to the nearest inch at entry to the study, was used to calculate BMI for each weight recorded. BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2).

A binary variable indicating reported presence of diabetes mellitus was defined at each examination. Evidence for diabetes mellitus was sufficient if the disease was reported by the study member or his physician. Blood sugar levels have not been routinely measured and no details about control of diabetes have been collected.

Smoking histories were obtained retrospectively, for about 75 percent of the cohort using mailed questionnaires in 1974 and 1982. For study members who died before 1974, and for those who did not respond to either questionnaire, a detailed review of existing records from physician reports was conducted to obtain any information concerning smoking habits. Histories were retrieved where possible from clinical records, but remain unknown for 14 percent of the cohort. No assumption about smoking habit was made for these members. Four mutually exclusive categories were defined at each examination: never smoked, current smoker, former smoker, and unknown smoking status. During analysis, where the smoking variable was used, subjects whose smoking

status was unknown were not excluded from analysis, but rather were included in the unknown category.

4.2.4 Follow-up of the cohort

On July 1, 1948 the mean age of the 3,983 subjects of the MFUS cohort was 31.1 years with a standard deviation of 6.1 years. Most of the subjects, 87 percent, were between age 20 and 39 years at that time. The age distribution at entry to the study is shown in Table 4.1. By July 1, 1993, after 45 years of follow-up, 1691 subjects had died, at a mean age of 63.9. Of the remaining 2292 subjects, 2159 were known to be alive on July 1, 1993 and 133 study subjects, 3.3% of the cohort, are assumed to be alive only to the date of last contact. Thus, these 133 subjects have less than 45 years of follow-up. The mean age of those known and assumed to be alive on July 1, 1993 was 74.0 with a standard deviation of 4.4 years.

Table 4.1 Distribution of age at entry and status after 45 years of follow-up of the Manitoba Follow-up Study cohort.

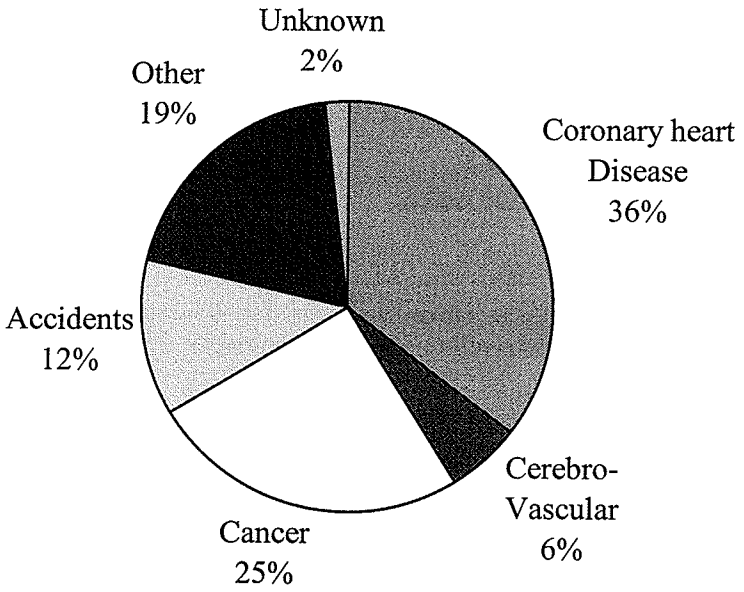
At July 1, 1948		Status at July 1, 1993		
Age (years)	Number of Subjects (%)	Alive	Dead	Unknown
18-19	12 (0.3)	10	2	0
20-24	336 (8.4)	235	88	13
25-29	1755 (44.1)	1173	519	63
30-34	1119 (28.1)	553	531	35
35-39	442 (11.1)	152	277	13
40-44	154 (3.9)	27	121	6
45-49	72 (1.8)	4	67	1
50-54	77 (1.9)	5	70	2
55-59	15 (0.4)	0	15	0
60-62	1 (0.0)	0	1	0
Total	3983 (100.0)	2159	1691	133

4.2.5 Mortality experience of the cohort

The distribution of cause of death of the 1,691 men who died during the 45-year follow-up is shown in Figure 4.1. Cause was attributed in 36% of deaths as due to coronary heart disease, of which 29% were due to ischemic heart disease and 7% other coronary heart disease causes. A further 6% of deaths were due to stroke, resulting in a total of 42% of deaths due to cardiovascular causes. One quarter of all deaths were due to cancer, 8% to aircraft accidents, 4% to other accidents, 19% to other causes and 2% with insufficient documentation to code cause of death. This distribution is strikingly similar

to the distribution of cause of death for other Canadian males. A distinguishing difference, however, is the proportion of deaths due to accidents, primarily increased in the MFUS cohort due to aircraft accidents.

Figure 4.1: Distribution of cause of death of the MFUS cohort



The mortality experience of MFUS cohort was compared to the mortality expected based on the rates observed in the Canadian male population. Indirect standardization methods using the age-specific Canadian male mortality rates reported in 5-year age intervals annually since 1948 were used to determine the number of expected deaths when applied to the MFUS cohort. The cumulative Standardized Mortality Ratio (SMR) since 1948 was calculated as the ratio of observed to expected number of deaths

and presented in Table 4.2. SMRs close to 1.00 in the early years reflect mortality rates of the cohort similar to those reported by Statistics Canada for the male population of Canada. Higher SMRs in the early years may be due to aircraft accidental deaths. During the early years of the study after WWII some study members remained in aviation occupations and worked as pilots flying in the north, at a time and place where fatality from aircraft accidents was high. The consistently lower SMRs during the later years of this study are indicative of a continuing favourable mortality rate for this cohort relative to other males in Canada.

Table 4.2 Cumulative mortality experience of the cohort at five year intervals throughout the 45-year follow-up period.

Year	Person years of observation	Observed number of deaths	Expected number of deaths	Standardized Mortality Ratio
1953	21808	53	57.9	91.6
1958	41302	127	123.1	103.2
1963	60383	209	217.3	96.2
1968	78912	353	360.4	97.9
1973	96692	500	567.7	88.1
1978	113518	741	852.0	87.0
1983	129115	981	1207.3	81.2
1988	143130	1331	1648.6	80.7
1993	153802	1691	2126.7	79.5

4.2.6 Selection of examinations for analysis

There are 92,060 examinations including blood pressure and or body weight measurements recorded and stored on file from recruitment to the RCAF during the early 1940s, during WWII, and from entry to the study up to July 1, 1993. The examination designated as the baseline examination for this analysis was the examination recorded closest to July 1, 1948. Age in years was calculated at each examination as the number of days from birth to the examination date divided by 365.25. In instances where only month and year were recorded on a report, the 15th day of the month was assumed for calculations.

Including the baseline examination, but excluding all other examinations recorded prior to July 1, 1948, a total of 76,509 examinations were identified for analysis during the 45-year follow-up period to July 1, 1993. This is an average of 19.2 examinations per study member. Only examinations prior to onset of IHD were retained for this analysis. The examination closest to each five-year birth anniversary, between ages 25 and 75 years, was selected as the index examination for that age. All selected examinations could be within 2.5 years of only one of the five-year birth anniversaries. Thus, a selected index examination could only be used once for a five-year birth anniversary examination in this analysis. After the exclusion of examinations recorded following onset of IHD, and exclusion of the examinations not closest to a five-year birth anniversary, 26,643 examinations were selected for analysis, an average of 6.7 examinations per study member.

The number of selected examinations and reasons for missing examinations are shown in Table 4.3. The potential number of examinations at each five-year age between 25 and 75 years was determined based on the age of each subject at entry in 1948 and their age as it would be in 1993. Men younger than 25 years of age at entry, for example, would not yet reach their 70th birthday by the end of the 45-year follow-up period, and hence could not contribute an examination at age 70 or 75 years for this analysis. A subject might not complete an examination and be at risk for IHD at a specific age if he: 1) died before that age, 2) was lost to follow-up before that age, 3) had developed IHD and was still alive before that age, or 4) if he was temporarily lost to follow-up for a period of time such that he was not examined within an interval of 2.5 years around the age. The last column of Table 4.3 contains the number of men with examinations and at risk of IHD at each five year age.

For example, the first row of Table 4.3 describes the subjects who could contribute an examination at age 25 years. Of the 348 men who were younger than 25 years of age at July 1, 1948, and hence eligible to contribute an examination at this age during the 45-year follow-up, 322 had an examination recorded within 2.5 years, and 26 did not. The 26 subjects who did not have an eligible examination at age 25 years were not lost to follow-up, and hence would contribute to examinations at older ages.

Study members who were lost to follow-up accounted 103 missing examinations. The largest number of missing examinations, 1,719, were not because of lost to follow-up, but rather due to subject who had intervals of time between examinations exceeding five

years, resulting in situations where no examination might be available within the 2.5 years around a 5-year birth anniversary. These 1,822 missed examinations are 6.4% of the possible examinations that could have been completed by subjects alive and free of IHD at the 5-year birth anniversaries.

Table 4.3 Distribution of number of examinations available for analysis. The examinations selected were prior to evidence of Ischemic Heart Disease and closest to and within a 2.5 year interval at each age.

Age	Younger than this age at end of follow-up	Older than this age at entry	Potential number of exam-inations	Reason for no examination at this age				Complete exam-inations
				Dead	Lost to follow-up	IHD (still alive)	Interval missed	
25	-	3635	348	-	-	0	26	322
30	-	1880	2103	9	-	0	233	1861
35	-	716	3222	47	-	2	295	2878
40	-	319	3664	90	-	20	173	3381
45	-	165	3818	154	-	70	79	3515
50	-	93	3890	244	-	145	58	3443
55	-	16	3967	364	-	240	82	3281
60	-	1	3982	548	4	341	112	2977
65	12	-	3971	812	18	428	266	2447
70	348	-	3635	1004	50	470	274	1837
75	2103	-	1880	790	31	237	121	701

Risk factors for IHD and each manifestation were modeled using the data from the examinations at each five-year age. All examinations selected had blood pressure recorded, but not all examinations had body weight recorded. The number of incident IHD events following these ages is presented in Table 4.4. The number of examinations at each age for modeling endpoints, available with and without body mass index included in a model are presented separately in this Table. Examinations with body weight not recorded were most prevalent in the later years of the study. At age 55 years, 93% of examinations were complete with BMI. At ages younger than this the percentage of examinations with BMI was greater. At age 60 examinations with BMI dropped to 88%, to 79% at age 65, 75% at age 70 years and 74% at age 75 years. The proportion of subjects who developed IHD was similar at all ages for models with or without BMI missing BMI values. Hence, it may be inferred that subjects who did not have BMI recorded is independent of subsequent IHD status.

Table 4.4 Number of subjects at risk of Ischemic Heart Disease and the number of subjects developing each manifestation of Ischemic Heart Disease for models with and without inclusion of BMI, by age.

Age	Models	Number at Risk	IHD	AP	MI	SD
30	Without BMI	1861	422	175	198	49
	with BMI	1847	417	172	197	48
35	Without BMI	2878	730	296	354	80
	with BMI	2832	714	288	346	80
40	Without BMI	3381	874	359	407	108
	with BMI	3308	850	346	399	105
45	Without BMI	3515	911	384	421	106
	with BMI	3446	888	375	410	103
50	Without BMI	3443	848	354	387	107
	with BMI	3300	809	339	369	101
55	Without BMI	3281	733	316	324	93
	with BMI	3042	672	289	297	86
60	Without BMI	2977	563	236	256	71
	with BMI	2623	483	199	226	58
65	Without BMI	2447	342	140	161	41
	with BMI	1930	272	112	129	31
70	Without BMI	1837	161	57	84	20
	with BMI	1384	124	41	71	12
75	Without BMI	701	55	18	31	6
	with BMI	516	42	13	24	5

5 STATISTICAL METHODS FOR LONGITUDINAL STUDIES OF CARDIOVASCULAR DISEASE

Longitudinal studies of CVD involve the collection of data from individuals over time. Data collected in a prospective cohort study includes baseline information at entry to the study, and data generally recorded at regular or irregular time intervals throughout the follow-up period. Baseline information will generally include demographic data including age at entry, gender, and contact residence. Determination and classification of clinical events, both CVD and comorbid non-cardiovascular conditions as they occur, time under study at each examination or clinical event, time last known to be alive are recorded concurrently throughout the study period.

Hence key considerations of any epidemiologic analysis of a follow-up study of CVD will include: 1) definitions of CVD events, 2) risk factor definitions, 3) description of CVD occurrence times, 4) statistical methods for testing of hypotheses concerning the association of risk factors and CVD (Glenn 1977).

5.1 Definition of cardiovascular disease outcomes

A definition of each CVD event, or endpoint for analysis, needs to be clearly stated prior to analysis. Often cardiac and non cardiac coronary heart disease events will be of interest. Endpoints defining CVD morbidity may be restricted to IHD defined by myocardial infarction, angina pectoris and sudden death, or may also include other non-

ischemic coronary heart disease. Studies may accept reports from subjects as sufficient, or require supporting evidence from physicians or hospitals. The strength of the evidence and source should be included in an analysis and a description of varying strengths of evidence of CVD is appropriate. Some follow-up studies of CVD include cardiac surgery as an endpoint. All cause mortality and deaths due to cardiovascular disease are recorded. For all these events, it is critical to record the date and details of each episode.

5.2 Definition of risk factors for cardiovascular disease

Risk factors for CVD are those characteristics of individuals thought to or hypothesized to be related to an increased likelihood of CVD. Risk factors play a crucial role in understanding the development of CVD, and risk factors for one endpoint of CVD may not necessarily be associated, nor carry the same strength of association for another manifestation of CVD. Risk factors in follow-up studies of CVD may involve characteristics or factors that are determined once and have a fixed value throughout the follow-up study. Factors measured once and fixed in value for the duration of the study, include gender, genetic characteristics, a predisposing family history of CVD and evidence of comorbid conditions at entry to the study. Also, this would include baseline measurement of blood pressure or body build or lipid profile that could be related to subsequent development of CVD. Alternatively, characteristics may be measured repeatedly over time, and hence be "time-dependent". Typical characteristics measured over time in follow-up studies of CVD have included repeat measurement blood pressure,

lipid determinations, body build, detection of coexisting disease conditions, smoking habit, abnormalities recorded on routine electrocardiograms and activity.

5.3 Time of occurrence of cardiovascular disease

The occurrence of CVD is a dynamic process documented over time during the study. A basic concept for the description of time under study is the "person year of observation" (Breslow 1984). One person year of observation will be accrued and contributed to an analysis for each year a study subject is alive and under observation. Also, for each six months two subjects are observed, one person year of observation is contributed. The total person years of observation each subject contributes to an analysis of CVD is the time (in years) from entry to the study (time zero) to the earliest of: determination of a first CVD event, date of a subject's last contact or date of withdrawal from the study subject, date of death, or date of termination of the study.

As new CVD events occur, the ratio of the number of new events in a specified time period, or age category, to the number of subjects alive and under study is the incidence of CVD. The incidence of CVD is therefore the rate of development of new events among those not previously diagnosed. Incidence density of CVD is calculated per person year of observation during the interval of follow-up.

The prevalence of CVD is defined at any point in time as the proportion of subjects alive and known to have CVD divided by the number of subjects known alive and under observation at that time. Consequently, the prevalence of CVD will change

with time and is influenced both by the incidence of events being documented and the length of time subjects with known CVD survive.

Hence, the incidence measures rate of new CVD events experienced by the cohort and the prevalence measures the burden or extent of CVD being experienced by the cohort under study at a point in time. Rates of CVD can be compared between groups by calculating incidence or prevalence rates for different subgroups of one cohort. A problem with the direct comparison of rates may arise because the groups may have very different age structures, and hence differences in the rates may just be reflecting these age differences. Techniques for "standardizing rates" are available so that the adjusted rate reflects the CVD experience to be expected if the groups being compared had the same age structure (Rothman 1986).

Variation in CVD rates over a long follow-up period may be influenced by the effects of aging, effects due to the period of time rates are determined or effects due to characteristics of individuals born at different points in time (Kupper et al. 1985, Holford 1991, Holford 1992, Wolinsky 1993). Variation introduced to rates by the aging process are termed age effects. Variation due to experiences of individuals at points in time or secular changes in rates are called period effects. Differences between groups of subjects who were born at different points in time and hence have had different experiences as a group are called cohort effects. There is no way of estimating all three effects simultaneously as specification of two effects determines the third. When two of the three effects are considered in an analysis, the third would be redundant (Robertson et al.

1999). Incidence and prevalence of CVD can be described within strata defined by birth cohorts and within age groups over calendar period of time.

In addition to describing the incidence and prevalence of CVD experienced by the cohort, there is also interest in describing for a subject, the probability of development of CVD over a defined period of time. Survival analysis encompasses mathematical techniques used to describe the experience over time of the cohort (Crowley and Breslow 1984, Prentice and Farewell 1986). For each study member, time from entry to the CVD event or time to end of follow-up is known. This interval of time is called the "survival time" and in the terminology of survival analysis of CVD is synonymous with "time to CVD event". For each survival time there is also an indication of whether the time is to an observed CVD event, or the time is to end of follow-up without a CVD event observed.

Time to event data have two unique characteristics. Firstly, the distribution of observed time to event tends to be skewed to the right and hence does not follow a normal distribution. Secondly, some events may not occur until after the end of the study, and hence times are not observed during the defined follow-up period. These event times reflect the follow-up time for a subject who has not experienced CVD by the end of the subject's time under study. Such event times are termed censored. All that can be said about time to CVD for censored follow-up times is that the time to CVD is unknown, but would be longer than the follow-up time observed thus far. Hence, the arithmetic average of observation times for all subjects does not equal average time to

CVD in the presence of censored observations. However, median survival time is often calculated and reported (Collett 1994).

There are three mathematical functions that define the survival characteristics of a cohort: the probability density function of survival time, the survival function and the hazard function.

Define: T as the random variable representing survival time, $T > 0$

t as the actual survival time of an individual, $t > 0$

Denote the underlying non-negative probability density function of T by: f(t). The distribution function of T is denoted by: $F(t)=P(T<t)$, where "$P(T<t)$" is read as "the probability that the random variable T, survival time, is observed to be "t" units of time or shorter". Thus, $S(t)=1-F(t)$ is the probability of surviving at least as long as "t" units of time. The hazard function, h(t), is the instantaneous probability of an CVD event at time "t", conditional on surviving to that time. The cumulative hazard function, H(t), is the integral of h(t) over all survival times up to time t and represents the accumulated instantaneous chances of a CVD event up to time "t".

These three functions are related to one another, such that

$h(t) = f(t) / F(t)$ and $S(t) = \exp(-H(t))$ and $H(t) = \ln(-S(t))$

5.4 Statistical considerations concerning the association between risk factors and cardiovascular disease

A coronary heart disease risk factor is any measured variable or characteristic that predisposes an effect on the likelihood or risk of CVD (Greenberg and Kleinbaum 1985). The scale of measurement of a risk factor might be binary (gender), categorical with no ordering to the categories (region of residence), categorical with an ordinal scale (education; less than high school, high school, college) or continuous (age in years). The outcome variable can be represented simply as a binary indicator of whether CVD occurred during the follow-up interval, or as the time to detection of CVD, (or time of follow-up for censored observations). Many statistical techniques are available for analysis of the association between risk factors and CVD depending on whether one or several risk factors are examined; whether confounding variables are known and measured and hence need to be controlled, whether risk factors are measured as binary, categorical or continuous variables, and whether the CVD outcome is defined as occurrence of an event or time to an event. Table 5.1 summarizes some statistical approaches for the examination of the association between risk factor(s) and CVD outcome in longitudinal studies.

Table 5.1 Statistical methods for the examination of the association between risk factors and cardiovascular disease in longitudinal studies

Type of Risk Factor(s)	Binary indicator of CVD during follow-up / statistical test	Time to CVD / statistical test
One Binary	Odds Ratio / Chi-square test	Kaplan Meier Curves / Logrank or Wilcoxon test
One Categorical (unordered)	Odds Ratios relative to reference category/ Chi-square test	Kaplan Meier Curves / Logrank or Wilcoxon test
One Categorical (ordered)	Odds Ratios relative to reference category / Chi-square test for trend	Kaplan Meier Curves / Logrank or Wilcoxon test
One Binary with One Categorical Confounder	Mantel Haenszel / Chi-square Test	Cox Proportional Hazard Model
Continuous, with or without other binary or categorical	Logistic Regression Model	Cox Proportional Hazard Model

5.4.1 Kaplan–Meier estimate of the survival curve and the log rank and Wilcoxon tests

A mathematical technique for describing the survival experience of a cohort based on the cumulative product of the conditional probabilities of survival to each observed event time was developed by Kaplan and Meier (Kaplan and Meier 1958). This has come to be referred to as the Kaplan-Meier or product limit estimate of the survival curve. It is

a useful method to describe the probability of developing CVD, or conversely, remaining free of CVD, to a point in time during the follow-up interval.

If "k" distinct event times are observed during the follow-up interval, denote by:

t(1), t(2), t(3), the CVD event times, and

n(1), n(2), n(3), the number of subjects at risk of CVD just before an event occurs, and

d(1), d(2), d(3), the number of events observed at each event time

then d(k)/n(k), the value of the hazard function, is the probability of a CVD event at time t(k) conditional on surviving to time t(k). The product of all the individual conditional probabilities up to the k^{th} event time, the cumulative hazard function, is the probability of surviving to time t(k). This survival function can be plotted against time and takes the form of a "step function", where its value remains constant between observed events and then "steps down" to a lower cumulative survival probability as each event is observed. To compare the survival distributions of two or more groups of subjects based on categories of risk factors one approach is to calculate the Kaplan - Meier estimate for each category and compare the curves. The log-rank test is a chi-square test with 1 degree of freedom used to test for significant differences in survival between the groups. This test is most appropriate if the hazard functions for the groups are proportional, and the survival curves for groups do not cross over. Alternatively, the Wilcoxon test for differences in survival distributions can be used. The Wilcoxon test is a weighted version

of the log rank test, and gives more weight to differences early on between the groups, when the number of subjects in groups are the greatest and differences are less subject to variation due to smaller number of subjects.

5.4.2 Odds ratios

A binary risk factor is often an indicator of the presence or absence of a characteristic. Denote by p_1 the proportion of subjects with the characteristic who developed CVD and denote by p_2 the proportion of subjects without the characteristic who developed CVD by the end of follow-up. The odds of CVD in subjects with the characteristic is $p_1 / (1-p_1)$; and the odds of CVD in subjects without the characteristic is $p_2 / (1 - p_2)$. The ratio of these two odds, $(p_1 / (1 - p_1)) / (p_2 / (1 - p_2))$, is the odds that a subject with the characteristic will have developed CVD relative to the odds that a subject without the characteristic will have developed CVD during the follow-up period. Confidence intervals can be calculated to provide an estimate of the degree of precision of the odds ratio, and the statistical significance of the odds ratio can be assessed with a chi-square test (Mantel 1963).

When a characteristic is categorical, with k categories (k>2), the concept of the odds ratio can be easily extended. The odds of CVD for those in category "i" is $p_i / (1 - p_i)$. Thus the odds of CVD for those in category "i" relative to a referent category "o", is $(p_i - (1 - p_i))/(p_o / (1 - p_o))$. The chi-square test with k-1 degrees of freedom is used to test for association of the variable with CVD. If the categorical variable is ordinal, the chi-square test for trend can be used.

5.4.3 Mantel-Haenszel chi-square test

Control for confounding is an important consideration in epidemiologic analysis. When examining the association between a binary risk factor and CVD, a third categorical variable related to each of the other two may influence the estimate of the odds ratio measuring the effect of the risk factor on CVD. One approach to account for this potential confounding effect is to stratify on the third variable, and estimate the odds ratio within each stratum. If the odds ratios are homogeneous across strata (Breslow and Day 1980), the Mantel Haenszel procedure (Mantel and Haenszel 1959, Mantel 1963, Mantel 1966, Kuritz et al. 1988) can be used to estimate a summary odds ratio combining the estimates of the odds ratios from each strata and effectively eliminate the confounding influence of the third variable on the relationship between the risk factor and CVD.

5.5 The General Linear Model

A model is a simplified description of reality (Hassard 1991). A statistical model is a mathematical function describing the link between an outcome and some explanations for the outcome. The general linear model is the basis for the simplest modeling approach to data as it describes a linear relationship between the outcome (dependent variable) and some predictor(s) (independent variable(s)) thought to influence the outcome.

The general linear model describing a straight line relationship between two continuous variables is of the form:

$$y = \alpha + \beta x + \varepsilon$$

where

x is the independent variable

y is the dependent variable

α is the intercept

β is the change in y for an incremental unit change in x

ε is the error term representing the residual difference between the outcome observed for an individual and the outcome estimated by the model.

This model can be easily extended to the multivariate case where "k" variables can be modeled to predict an outcome as follows:

$$y = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k + \varepsilon$$

where y, the outcome variable, α, the intercept and ε, the residual term are as above, and

x_i is one of "k" independent variables

β_i is the change in y for an incremental unit change in x_i $i = 1,\ldots,k$

The assumptions for the general linear model to be valid are: 1) that "y" be a continuous scaled variable, 2) with a normal distribution, 3) that the relationship of the predictor variable "x" with "y" be reasonably linear, 4) that the residuals, ε, be equally distributed above and below the fitted line, and 5) that "y" have a constant variance along the range of "x". Statistical methods have been derived to determine the best estimates of the parameters of this model (Hassard 1991).

5.6 Modeling Binary Outcomes

While the general linear model is well suited to exploring the relationship among many CVD risk factors, for example prediction of blood pressure as a function of age or body weight, it is ill suited to the epidemiological analysis of survival data.

It may be of interest when analyzing longitudinal data to develop a model, similar to the general linear model, that relates values of independent variable(s) measured to a subject's likelihood or chances of CVD. For the moment, disregard time to CVD, and denote presence or absence of CVD in the follow-up interval as "1" for those who develop disease and "0" for those remaining free of CVD. This defines those who "definitely develop CVD" with probability "1" and those who "definitely do not develop CVD" as probability "0". With these values for presence or absence of CVD, the probability of developing CVD could be modeled as a linear function of predictor variables (Collett 1994).

5.6.1 Linear Probability Model

If the general linear model is used with "probability of CVD in follow-up period" modeled as the outcome variable, then

$$\Pr(CVD=1) = y = \alpha + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k + \varepsilon$$

is called the linear probability model.

While this model could be fit to the data, with 0 or 1 as the only values of the outcome variable, there are serious violations of the assumptions required to use the general linear model and erroneous interpretations would result. It would be possible in

some instances that values predicted from the model would lie outside the acceptable range, i.e. for some combinations of risk factors the probability of CVD could be predicted to be less than zero or greater than one. Further, the outcome variable is not continuously scaled, and does not have a normal distribution, but rather, it has a binomial distribution (Khan and Sempos 1989).

5.6.2 Logistic Regression Model

The logistic regression model has become a standard model for the analysis of binary outcome data in epidemiological studies (Walker and Duncan 1967, Greenland 1979, Green 1988, Hosmer and Lemeshow 1989). The multivariate analysis of CHD data from the Framingham Study was first modeled with the logistic regression model in 1967 (Truett et al. 1967). Prediction models for the occurrence of CHD were developed using this model in the analysis of the Framingham data (Gordon 1974, Gordon and Kannel 1982). The motivation for logistic regression comes from the appeal of the linear probability model and recognition that while there are violations of assumptions, in mid ranges of probabilities for CVD, a linear fit seemed reasonable, but that the lower and upper tails of the distribution, i.e. at particularly low or high levels of risk of CVD, were not fit well to a linear model. So, rather than a linearly increasing model for probability of disease, with increasing value of risk factors, a sigmoidal curve was postulated that would flatten out both at the lower end and the upper end, i.e. at lower and higher levels of risk factors. This was consistent with the notion that an incremental increase in risk

factor levels in the mid range would have a proportionately larger effect on risk of CVD, than the same magnitude of change might have at either tail.

The logistic regression model describing the relationship between "p", the probability of CVD in the follow-up interval, and a set of "k" predictor variables is given by:

$$p = P(CVD) = 1 / (1 + \exp(-(\alpha + \beta_1 x_1 + \beta_2 x_2 + ... + \beta_k x_k)))$$

which is algebraically equivalent to :

$$\ln (p/(1-p)) = \alpha + \beta_1 x_1 + \beta_2 x_2 + ... + \beta_k x_k$$

where p/(1-p) is the odds of CVD, and ln(p/(1-p)) is the natural logarithm of the odds. Therefore, the logistic regression model equates the log of the odds of CVD as a linear function of a sum of weighted predictor variables. The weights for this model, b_i , are estimates of the parameters, β_i , and are called the logistic regression model coefficients.

The probability of CVD ranges from 0 to 1. Hence, the odds of CVD ranges from 0 to infinity, and the ln(odds of CVD) from minus infinity to plus infinity. Risk factors with a positive association to CVD have positive coefficients, while those inversely related to CVD have negative coefficients. The weighted sum of the linear function of predictor variables in the model is called the prognostic score and can range from negative values through zero to positive values. The larger the prognostic score, the greater the probability of CVD (Chambless et al. 1990).

The logistic regression model equates the natural logarithm of the odds of CVD to the prognostic score, S, (Hosmer and Lemeshow 1989). Hence the relationship of these concepts:

the natural logarithm of the odds of CVD = S

the odds of CVD = exp(S)

the probability of CVD = 1 / (1 + exp(-S))

Denote the prognostic score for one subject with a set of characteristics in a logistic regression model by S1 and for a second subject with a different set of characteristics by S2. Thus, the odds of CVD for subject 1 is exp(S1) and for subject 2 is exp(S2). The relative odds of CVD, or odds ratio, for subject 1 relative to subject 2 is exp(S1) / exp(S2) = exp(S1-S2). If subject 1 and subject 2 differ in only one characteristic included in the model, say variable x_j a binary indicator coded as "1" for its presence in subject 1 and "0" for absence in subject 2; then the prognostic scores of the two subjects will differ only by a the value, "b_j", and the relative odds of CVD for subject 1 relative to subject 2 will be exp(b_j). Thus, each coefficient in the multiple logistic regression model represents the contribution of each variable to the prognostic score. The exponential of the coefficient represents the relative odds of CVD in two subjects who differ only by one unit in that characteristic, all other variables being equal. The exponential of the regression coefficient from a model with one binary independent variable is therefore analogous to the univariate odds ratio calculated from the "two-by-

two" layout described earlier and tested with a chi-square statistic. The exponential of a coefficient from a binary variable in a model including other variable(s) as well, is interpreted as an "adjusted odds ratio", analogous to the adjustment of the Mantel-Haenszel procedure for combining information from a series of "two-by-two" tables.

The logistic regression model has been applied in CVD research (McGee et al. 1984, Abbott and Carroll 1984, Abbbott 1985, Harrell and Lee 1985, Hosmer and Lemeshow 1989) and remains the model of choice to relate "baseline" characteristics to CVD in a defined follow-up interval of fixed duration (Wu 1979). The model has been extended to incorporate inclusion of updated covariate values as information was obtained from subjects over time (Wu and Ware 1980, D'Agostino et al. 1990).

5.7 Modeling time to event

5.7.1 The Poisson Regression Model

Time to event data may be summarized and reported at an aggregate level, perhaps within strata defined by age categories. For the subjects within each strata, the total number of CVD events observed over the follow-up period represent a numerator and the total person years of observation for all subjects in the strata represent a denominator. The ratio of these two numbers is an estimate of the CVD rate incurred by subjects in the strata. If CVD events are assumed to occur independently, that is the occurrence, or not, of CVD by one subject in a strata in no way influences the occurrence of CVD by another subject, and the number of CVD events recorded typically is small,

relative to the total number of person years recorded, the assumption of a Poisson probability model is reasonable (Woodward 1999).

A Poisson regression model may be specified where age categories are represented by binary indicators. After estimation of the parameters and their standard errors, the statistical significance of these indicators would provide evidence for varying rates of CVD by age. It should be noted that the data need not necessarily be specified at an aggregate level. If follow-up time and a binary indicator for the CVD event at the end of follow-up is known for each subject, a Poisson regression model can also be fit. Hence, the Poisson regression model can accommodate continuous or categorical independent variables measured at the individual level as well.

5.7.2 The Cox Proportional Hazard Model

While logistic regression has been widely used to model CVD occurrence in a follow-up interval, for epidemiological analysis of longitudinal data, this model has limitations for dealing with varying follow-up time from subject to subject and censoring of observations (Kalbfleisch and Prentice 1980, Allison 1985). In 1972, Sir David Cox introduced the proportional hazards (PH) model to provide a link between the hazard function , h(t), or survival function, S(t), and a set of covariates of individuals (Cox 1972, Cox 1975).

The PH model relates the hazard function at time "t" to a set of "k" covariates measured in individuals as follows:

$$h(t) = h_0(t) * \exp(\beta_1 x_1 + \beta_2 x_2 + ... + \beta_k x_k)$$

where $h(t)$ is the hazard function at time t

$h_0(t)$ is the baseline hazard function for a subject with zero values for all covariates

$\beta_1, \beta_2, ..., \beta_k$ are the "k" regression coefficients

$x_1, x_2, ..., x_k$ are the values of the "k" covariates

Hence, $h(t) / h_0(t) = \exp(\beta_1 x_1 + \beta_2 x_2 + ... + \beta_k x_k)$ and

$$\ln(h(t) / h_0(t)) = \beta_1 x_1 + \beta_2 x_2 + ... + \beta_k x_k$$

Thus, the PH model equates the natural logarithm of the ratio of the hazard function at time t and the baseline hazard function to the weighted sum of predictor variables. As before, the weights are regression coefficients obtained by maximum likelihood estimation from the observed data and are called Cox PH model regression coefficients.

This weighted sum is again a prognostic score and differences in prognostic scores that arise from different covariate values for subjects can be interpreted in a similar fashion to those for logistic regression, however, not as relative odds, but as relative hazard, or relative risk of CVD (Prentice et al. 1982). In the logistic regression model, the natural logarithm of the odds of development of CVD is a linear function of covariate values, and the exponential transformation of the coefficients for a variable in this model reflects the relative odds of CVD, for a unit change in the independent variable. In the

Cox PH model, the exponential transformation of a coefficient reflects the effect of a unit change in the independent variable on the relative rate or relative hazard of development of CVD over the follow-up interval (Cox 1972, Cox 1975, Breslow 1975, Kay 1977, Andersen 1991, Prentice and Kalbfleisch 1979). An essential difference in the two models is that in the PH model there is consideration for time to events, adjustment for varying follow-up periods and compensation for censoring of observations (Kalbfleisch and Prentice 1980, Allison 1985). An important assumption concerning censoring is that the censoring mechanism be independent of CVD. The assumption implies that the reason for a subject being lost to follow-up was not related to the individual's likelihood of developing CVD (Collett 1994).

A key assumption of the Cox PH model is that the ratio of hazards be constant, or proportional, value at all points in time. A binary covariate, for example presence or absence of hypertension, might relate to two fold increased risk of CVD for a hypertensive subject relative to non-hypertensive throughout the follow-up period. Although the hazard, i.e. instantaneous risk, of CVD may be changing with time, this two fold increased risk (for hypertensive relative to non-hypertensive subjects) is assumed to remain throughout the follow-up interval. This assumption can be verified by graphical methods or by examining covariates as functions of time under study in the PH model (Kalbfleisch and Prentice 1980, Collett 1994).

Variations of the PH model have been proposed to compensate for violations of the proportion hazard assumption. If subsets of a population have different underlying

risks of CVD, perhaps due to regional variation in rates of CVD, a stratified PH model can be fit where a different hazard function in each region is specified in the likelihood function but a common effect within each region for each variable is estimated for a covariate (Kalbfleisch and Prentice 1980, Collett 1994).

The effects of time dependent covariates can be modeled with the Cox PH model. Time dependent covariates are variables that represent changing values of covariates measured at repeat observation of subjects over time (Chang et al. 1990, Andersen 1992), or they can be binary variables that can change in value over time to reflect presence or absence of characteristics detected over time. The PH model has become the most widely used model in analysis of longitudinal studies of CVD due to its ability to accommodate fixed time and time dependent variables and the appeal of not having to specify an underlying hazard function.

5.7.3 Parametric Survival Models

One appealing feature of the Cox PH model, other than the ability to relate covariates to the relative risk of CVD, is that the underlying hazard function remains completely unspecified. The PH model can be used for analysis of survival data from cohort studies with any underlying risk of CVD as long as the proportionality assumption for covariate effects is reasonable. Because the hazard function is unspecified, but the relationship between the hazard function and covariates is specified, the PH model is often referred to as a semi-parametric model (Collett 1994). If the distribution of survival times does follow a recognizable form, such that the probability density function and

hence hazard function is known, then a parametric model can be used. The estimates of coefficients for the covariates will have smaller standard errors and inferences concerning them will be more precise. The simplest example of a parametric model for survival is one where the hazard function is constant over time. This characterizes the exponential distribution where a constant hazard implies CVD events are occurring at the same rate along a time axis as the cohort ages. Over short intervals of time, for a cohort with a narrow age range this may be justifiable, but in general this does not seem to fit well with the natural course of CVD. Perhaps a more realistic assumption is that the hazard function is increasing with time and that as the cohort ages, the instantaneous risk, or underlying rate of CVD is increasing. This form of hazard function is characteristic of the Weibull distribution and has been used with the Framingham data (Andersen 1991, Odell et al. 1994).

5.8 Other analytic considerations for modeling cardiovascular disease

General methodological advances for statistical modeling of epidemiologic data have been recently reviewed (Gail 1991, Cox 1993, Henderson 1995). The role of the logistic regression model and the Cox PH model are central to this discussion and both models add to the understanding of risk factor and outcome relationships in well designed longitudinal studies of CVD.

The logistic regression model and the Cox PH model have proven to be very useful for modeling data from longitudinal epidemiologic studies of CVD. Under certain

conditions the two models produce very similar results. If the effect of interest, i.e. the odds ratio or hazard ratio, is small; if the follow-up period is relatively short so that the risk of CVD changes very little over time and the rate of withdrawal of subjects is low; and the absolute risk of disease in the cohort during the period of follow-up is low, say less than ten percent, then the two models will provide similar results (Green and Symons 1983, Abbott 1985, Peduzzi et al. 1987).

How well a general linear model "fits" the data is measured by the proportion of variation in the dependent variable that is "explained" by the predictor variables (Hassard 1991). With either the logistic regression model or the PH model, the dependent variable is a function of the development or not of CVD, and as such the concept of explained proportion of variability does not apply. Several alternatives for a "goodness of fit" measure have been suggested (Lemeshow and Hosmer 1982, Hosmer et al. 1991, Cox and Wermuth 1992, Mittlbock and Schemper 1996, Schemper and Stare 1996). The Hosmer-Lemeshow statistic (Hosmer and Lemeshow 1989) for the logistic regression model is widely used. Based on the chi-square statistic is a measure of the agreement between the number of CVD events observed to the number expected within deciles of risk determined from the prognostic scores of each subject. Various "explained variability" measures for the Cox PH model have been recently described (Schemper and Stare 1996). These measures are generally related to the value of the likelihood function in a model with covariates to its value when the null model (with no covariates) is fit. Some authors allow compensation for the number of parameters estimated.

The time scale used with the PH model is generally referenced to the time of entry to the study. Thus, the time axis relates to time under study and control for age differences in subjects is obtained by modeling age as one of the covariates. Alternatively age can be used as the time-scale, so that subjects at different ages at entry are realigned and are modeled with parameter estimation determined among subjects at the same age and not just at the same time under study (Korn et al. 1997). With this approach, calendar period and cohort effects can be controlled through stratification.

The power to detect significant effects using logistic regression models has been recently described (Hsieh 1989). Power is related to both the number of CVD events and the number of subjects at risk. If the independent variable is binary, power calculations are equivalent to those for the comparison or two proportions. For a continuous variable and a difference of one standard deviation unit, in cohort of 4,000 people with an underlying risk of 25% for CVD during the follow-up period, there would be an 80% chance of detecting an odds ratio greater than 1.10 at the 5% (one sided) level of significance.

5.9 Statistical Methods for Specific Objectives

5.9.1 Methodology for Objective 1 - Incidence of Ischemic Heart Disease

Incidence of IHD and its manifestations were calculated as number of first events per 1,000 person years of observation. Person years of observation free of IHD were calculated as the time under study from entry to the earliest of: date of detection of IHD,

date of last contact, date of death or June 30, 1993. Person years of observation and number of events were tabulated for 5-year age intervals. The incidence of IHD was calculated within these 5-year age intervals and tested for a trend with age using Poisson regression (Koch et al. 1986). Age-specific incidence was also calculated in this manner for AP, MI and SD. Only the first manifestation of IHD was considered. That is, after diagnosis of AP, for example, a first MI was not counted in the calculation of incidence of MI.

5.9.2 Methodology for Objective 2 - Patterns of risk factors by age and time

5.9.2.1 Determination of age-specific percentiles of risk factors

Including the baseline examination, all 76,509 examinations recorded during the 45-year follow-up period to July 1, 1993 were identified. The integer value of age at each examination was calculated. Only examinations prior to onset of IHD were retained. The age specific percentile distributions of SBP, DBP and BMI at all ages were determined. The "p^{th}" percentile of a distribution was defined as the cut point of the cumulative distribution of the variable such that at most "p" percent of all measurements recorded at that age were less than or equal to the cut point. Digit preference for recording blood pressure has been discussed as a potential problem in selection of cut points for determination of risk of disease in some studies (Wen et al. 1993), but this is not an issue for defining percentiles from the BP distributions based on the above definition. The percentile points for each age-specific distribution of SBP, DBP and BMI were used to

determine the percentile of SBP, DBP and BMI for each measurement in each subject's file.

5.9.2.2 Distribution of risk factors at 5-year birth anniversaries

For the analysis of patterns of SBP, DBP and BMI with age, the index examinations selected at the examinations closest to each 5-year birth anniversary between ages 25 and 75 years were used. Selection of these 26,643 examination was described in Section 4.3.6. Further, the time period of examination was classified by date of examination into 5-year intervals from July 1, 1948 through to June 30, 1993. The mean and standard deviation of SBP, DBP and BMI were calculated at each 5-year age from 25 to 75 years. Mean SBP, DBP and BMI were plotted for subjects of the same age group across calendar period of examination to discern variation in patterns over time.

The proportion of subjects examined at these ages with a history of diabetes mellitus was calculated. The proportion of subjects at these ages in different smoking categories was calculated to estimate smoking prevalence.

5.9.3 Methodology for Objective 3 - Tracking of continuous risk factors

Two measures of tracking were analysed for the serial measurements of SBP, DBP and BMI: the Pearson correlation coefficient and the relative likelihood of tracking.

First, the Pearson correlation coefficient was calculated to measure the strength of the linear association between the measurements of each risk factor at different ages. Correlation coefficients were calculated for measurements of SBP, DBP and BMI at pairs

of ages selected at the 5-year examinations between 25 and 75 years. The statistical significance of the correlation coefficient was assessed using the Student's t-test.

Second, quintiles of the distributions of SBP, DBP and BMI at the 5-year age examinations were cross tabulated throughout the follow-up period. The proportion of subjects moving to the top or from the bottom quintiles of the distributions at pairs of ages were used to quantify the degree of tracking at the extremes of the distributions. This evidence for tracking in the top SBP quintile between measurements at two different ages was defined as the proportion of subjects in the top quintile at the younger age who remained in the top quintile at the older age divided by the proportion of all subjects with examinations at both ages who were in the top quintile at the older age. This ratio, when greater than unity, measures the excess of individuals in the top quintile beyond what would be expected by chance if an individual's SBP level was a random phenomenon and no relationship existed between initial and subsequent SBP measurements. This ratio is a measure of tracking, and will be subsequently referred to as relative likelihood of tracking. The relative likelihood of tracking in both the top and bottom quintile for SBP, DBP and BMI was calculated for pairs of measurements at 5-year ages from 25 to 75 years. The statistical significance of the relative likelihood of tracking was assessed using a chi square statistic with 1 degree of freedom.

5.9.4 Methodology for Objective 4 - Modeling risk factors for Ischemic Heart Disease

The relationship between risk factors and IHD was examined from a number of perspectives. Incidence of IHD were plotted within risk factor categories at each 5-year age between 30 and 75 years. Risk factors at each 5-year age between 30 and 75 years were modeled using the Cox proportional hazard model. The proportionality assumption of the model was tested to determine whether the effect of a risk factor changed with time after measurement. Further, the varying effect of a risk factor at repeat measurement with age was examined using a time dependent covariate in the Cox model. Multivariate models were determined using a stepwise variable selection, to assess the importance of risk factors at different ages for IHD and each of its manifestations.

5.9.4.1 Trends in incidence of Ischemic Heart Disease within categories of risk factors

Person years of observation were determined from each 5-year age between 30 and 75 years to the earliest of date of IHD, end of follow-up or June 30,1993. The incidence of IHD per 1,000 person years was calculated within each quintile of the SBP, DBP and BMI distributions, for diabetics and non-diabetics, and within smoking categories from the selected examinations between 30 and 75 years in order to explore the impact of aging on the relationship between these risk factors and IHD. For SBP, DBP and BMI, the incidence ratio was defined as the incidence of IHD for those in the top quintile of the distribution divided by the incidence of IHD for those in the bottom quintile. For smoking or diabetes the incidence ratio is the incidence if IHD among

smokers (or diabetics) divided by the incidence of IHD among non-smokers (or non-diabetics). The incidence difference was defined as the difference in incidence of IHD between subjects in the appropriate two categories. At each age, the IR, the ID, and trends of IHD incidence across categories of each risk factor described the effect aging may have on the relationship of the risk factor with IHD.

Patterns of incidence of IHD, ID and IR were described for each risk factor. For the five risk factors, ID and IR described changing magnitude of effect with age. Patterns in incidence of IHD were described across the five quintile categories of SBP, DBP and BMI as increasing or decreasing without any formal statistical test for trend. The purpose of the calculation of incidence of IHD within these categories was to illustrate the patterns of incidence by age and risk factor category. Statistical testing for the significance of these risk factors for incidence of IHD both at specific 5-year ages and whether their effects were changing with age were assessed using the Cox proportional hazard model.

5.9.4.2 Age specific Cox proportional hazard models

Cox proportional hazard models for the development of IHD in the subsequent follow-up period were fit using observations at each 5-year examination age. An observed time to IHD was considered censored if the subject was still alive and free of IHD at June 30, 1993 or if the subject was lost to follow-up or died prior to the detection of IHD. The Cox model accounts for censoring and the unequal duration of follow-up that subjects will have due to age differences between subjects at entry to this study.

At each 5-year examination, the effect of each risk factor was estimated by including either SBP, DBP, BMI, a binary indicator for diabetes with non-diabetic as the reference category, or three binary indicator variables for smoking status: current smoker, former smoker and unknown smoking status with never smokers as the reference category. Secular trends in the incidence of IHD over the 45-year observation period were controlled by inclusion of year of examination in every model. The relative risk of IHD, with a 95 percent confidence interval, was calculated at each age for each risk factor. Relative risk was calculated for an increase of 10 millimeters of mercury (mm Hg) in SBP, a 10 mm Hg increase in DBP, a 5 kg/m^2 increase in BMI, for diabetics versus non diabetics and for smokers and former smokers versus never smokers.

5.9.4.3 Testing the proportionality assumption of the Cox proportional hazard model

Each variable included in a Cox model is assumed to have a constant effect on the hazard function, independent of time under study. That is, the relative hazard for subjects with different covariate values is assumed to remain constant at all time points during follow-up. This proportionality assumption was tested for each risk factor by determining the significance of the product term(s) in a model the representing interaction between each risk factor and the time under study. A significant interaction term would be indicative of a changing effect of the risk factor with time under study. The proportionality assumption was tested for each of the five risk factors from each 5-year examination.

5.9.4.4 Testing the varying effect of risk factors with age

The Cox proportional hazard model with time dependent covariates was used to examine the effect of aging on each risk factor. All 5-year interval examinations for each subject over the 45-year follow-up period were used to fit two models. For each risk factor, one model of main effects only, included year of examination, age at examination and the changing value of the risk factor from entry to the end of follow-up. The second model of main effects and the interaction term(s) of age with a risk factor, included year of examination, age at examination, the changing value of the risk factor, plus an interaction term, a variable equal to the product of age and the risk factor. This product term represents the interaction describing the varying effect of a risk factor with age over time. The significance of this interaction term was tested using the likelihood ratio chi-square test based on the difference of the value of the likelihood function of these two models. A statistically significant age and risk factor interaction term was considered evidence of a changing effect of the risk factor on IHD when measured repeatedly with age. Five pairs of models were systematically examined with interaction terms for age and SBP, age and DBP, age and BMI, age and smoking status and age and DM added to each model of main effects. This analysis was repeated for the AP, MI and SD endpoints. Reported p-values for variables in these models are based on two sided hypothesis tests.

5.9.4.5 Multivariate Cox proportional hazard modeling of Ischemic Heart Disease

The joint independent effect of risk factors at each age from 30 to 75 years were assessed by fitting multivariate models using a forward stepwise procedure. The best

fitting forward stepwise multivariate Cox proportional hazard models for IHD, AP, MI and SD were determined. Estimates of the relative risk of IHD with 95% confidence intervals were calculated for significant parameters. Year of examination was included in all models.

5.9.5 Methodology for Objective 5 – Contribution of tracking to models of Ischemic Heart Disease

5.9.5.1 Characterisation of individual risk factor patterns over time

For each subject, characteristics of the relationships of SBP, DBP and BMI with age, up to ages 50, 60 and 70 years were considered as possible additional risk factors for IHD. All measurements, not just the measurements selected at 5-year age intervals, for each subject from entry to age 50, 60 and 70 years, were used to characterize individual patterns for each continuous risk factor. The age-specific percentiles of SBP, DBP and BMI; denoted by SBP%ile, DBP%ile and BMI%ile respectively were used to account for the changing distributions of these variables with age. As described by Lauer (Lauer and Clarke 1988), parameters of the ordinary least squares regression of SBP%ile, DBP%ile and BMI%ile on age were used to describe the pattern of these measurements. This method is displayed in Figure 5.1.

Figure 5.1 Calculation of LEVEL, TREND and VARIABILITY

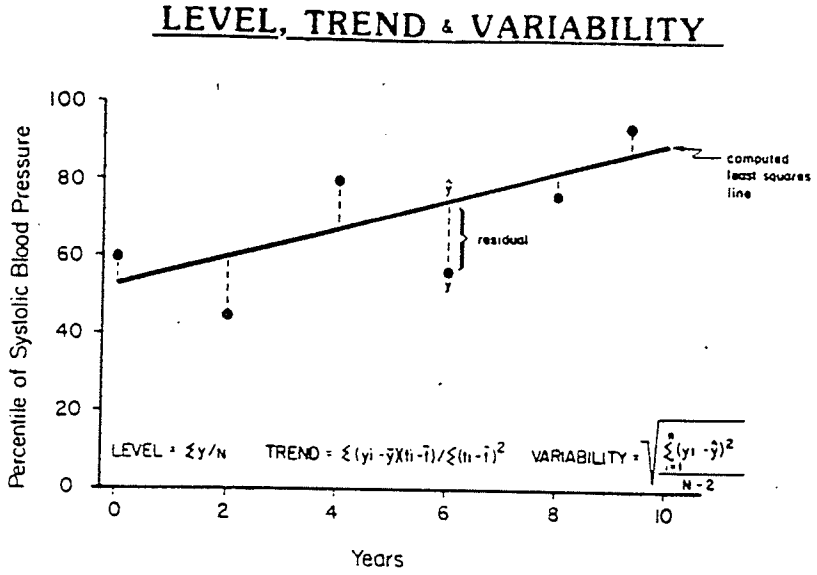


Figure 1. A hypothetical example of a single subject's systolic blood pressure percentiles observed over a ten year period In this example *level* of blood pressure is given by the average of the percentile of blood pressure in six observations; *trend* is given by the slope of the least squares line; *variability* is the square root of the sum of the squared residuals divided by *N*-2 (see text).

Adapted from: Lauer RM and Clarke WR. Statistics in Medicine 1988;7:p 49

For each risk factor, the mean of the percentiles of all measurements prior to the defining age was called level. Parameters of the regression line for each subject define the other two variables, trend and variability. "Level" is an indication of the average relative position for each subject in the age specific distribution of that variable at prior measurements. The slope of the ordinary least squares regression line of the percentile of each measurement on age was called trend. "Trend" with a negative sign, suggests a pattern of decreasing percentile rank over time for a subject, while a positive sign for trend suggests that an individual's rank relative to others at the same age has been

increasing with age. Trends close to zero suggest that a common percentile rank for the variable had been maintained over time, and did not change with age. A trend close to zero, therefore, is indicative of tracking. The root mean square error of the deviations about a regression line was called variability. High "variability" in the trend, reflected as a large root mean square error, is indicative of lability or changing, increases and decreases in BP or BMI. Low variability, indicates greater precision in the estimate of the slope of the line relating percentile with age.

5.9.5.2 Level, trend and variability of risk factors over time and Ischemic heart Disease

The combination of level, trend and variability may characterize subjects with different patterns of changing risk factors. Varying degrees of tracking may be characterized these combinations. The percentile distributions of the three measures, level, trend and variability, were determined for each variable and age combination. Deciles, tertiles and the median of these distributions were calculated.

Cox proportional hazard models for each of the four endpoints, IHD, AP, MI and SD, from age 50, 60 and 70 years of age were fit. Each "base" model included year of examination, SBP%ile or DBP%ile, BMI%ile, diabetes and smoking. The significance of tracking was tested by adding the continuous value of "level" and categories for "trend" and "variability" for each of SBP, DBP, and BMI to the base models. The likelihood ratio chi-square test was used to determine the significance of the contribution of tracking variables to these models.

6 RESULTS

6.1 Incidence of Ischemic Heart Disease and its manifestations

6.1.1 Age-specific incidence of Ischemic Heart Disease

All subjects were free of IHD at entry to the study. During follow-up, 1098 subjects developed clinical evidence of IHD. Subjects who developed IHD are described by first manifestation in Table 6.1. The first evidence of IHD was noted in 41% of cases (455 men) as AP, in 47% (515 men) as MI, and as SD in the remaining 12% (128 men). The mean age at IHD was 60.5 years with a standard deviation of 10.1 years. Mean age at each of the three manifestations varied by less than one year. Forty-one percent of cases, 452 men, 243 with AP and 209 with MI, were alive at end of follow-up.

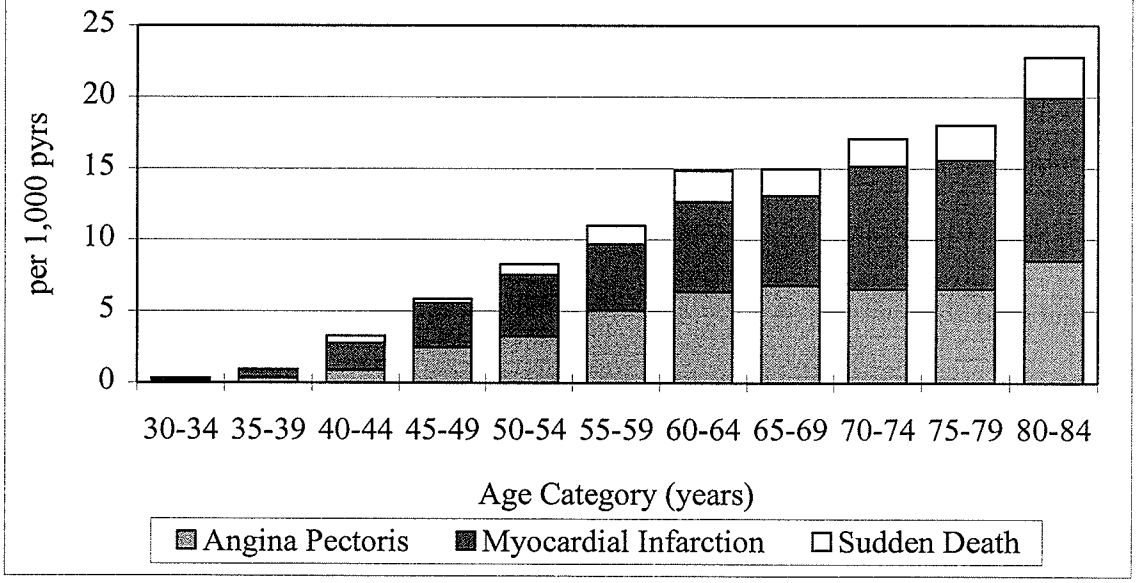
Table 6.1 Distribution of age at first manifestation of Ischemic Heart Disease

First Manifestation	Number (%)	Mean age ± standard deviation (years)
Angina Pectoris	455 (41.4)	60.7 ± 9.5
Myocardial Infarction	515 (46.9)	60.2 ± 10.6
Sudden Death	128 (11.7)	60.9 ± 10.1
All Ischemic Heart Disease	1098 (100.0)	60.5 ± 10.1

The age-specific incidence of IHD tabulated in five year age intervals over the 45-year follow-up period is shown by the height of each bar for each age interval in Figure

6.1. Incidence of IHD was low, less than 1 case per 1,000 person years (pyrs), before age 40 years. A rate of 3 new cases per 1,000 pyrs was observed for men age 40-44 years. The incidence of IHD rose steadily by about 3 cases per 1,000 pyrs with each 5-year age group up to age 65 years. Up to age 65 years, the incidence of IHD increased almost linearly with age. The incidence of IHD at age 60-64 years and age 65-69 years was equal, where after, after age 65 years incidence continued to increase with age, although at a slightly less steep rate than observed before age 60 years, to more than 15 new IHD cases per 1,000 men each year after age 70 years. The trend in incidence of IHD was estimated by the Poisson regression model. Incidence of IHD was estimated to increase between ages 30 and 84 years by 6.0% per year with a 95% confidence interval of 5.4% to 6.5%.

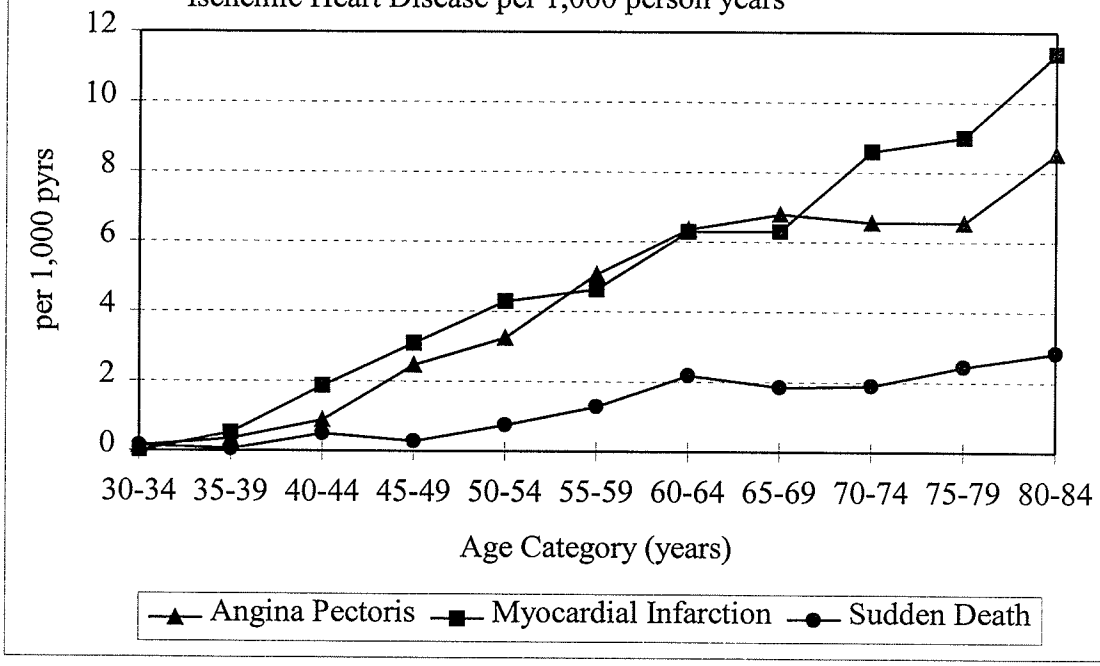
Figure 6.1: Age-specific incidence of Ischemic Heart Disease per 1,000 person years by manifestation



6.1.2 Age-specific incidence of Angina Pectoris, Myocardial Infarction and Sudden Death

The age-specific incidence of each manifestation of IHD is shown as a line graph in Figure 6.2. Incidence of AP and MI increased at about the same rate, one event per 1,000 pyrs, with each 5-year age group between ages 30-34 and 60-64 years. After age 65 years, the incidence of AP leveled off and remained at a rate of 6.5 new cases per 1,000 pyrs to age 80 years. The incidence of MI continued to increase beyond age 65 years to more than 10 new cases per 1,000 persons per year at age 80-84 years. Incidence of SD was lower than either that of AP or MI at all ages, remaining at about one third the rate of either AP or MI to age 65 years. Like the incidence of MI, the incidence of SD continued to rise with age after age 65 years.

Figure 6.2: Age-specific incidence of each manifestation of Ischemic Heart Disease per 1,000 person years



6.1.3 Summary of incidence of Ischemic Heart Disease

There were no prevalent cases of IHD at entry to the study. All 1098 IHD cases, 28% of the cohort, were documented as incident events during the 45-year follow-up period. No IHD events were documented before age 30 years. Incidence rose steadily with age. The age-specific incidence of AP and MI were similar up to age 65-69 years, where after, the incidence of SD and MI continued to rise with age. Incidence of AP leveled off at about 6 events per 1,000 pyrs after 60 years of age, and increased again at age 80 years.

6.2 Distribution of risk factors for Ischemic Heart Disease

As shown in Table 6.2, at examinations selected at 5-year age cross sections between 25 and 75 years, mean SBP increased from 120.9 mm Hg to 141.0 mm Hg. The standard deviation of SBP measurements also increased with age. This reflects the widening range of values of SBP recorded.

Mean DBP increased from 74.4 mm Hg at age 25 years to 82.5 mm Hg by age 55 years. After age 55, mean DBP levelled off to age 65 years, and dropped thereafter to 80.0 mm Hg by age 75 years. The increase, plateau and decline of mean DBP is mirrored by the standard deviation of DBP measurements.

Mean BMI increased from 22.7 kg/m^2 at age 25 years to 25.6 kg/m^2 at age 50 years. Mean BMI remained constant through to age 65 and decreased thereafter. The

standard deviation of BMI measurements tended to increase with age, even when mean BMI stopped increasing, reflecting largely the widening range of values of BMI with age.

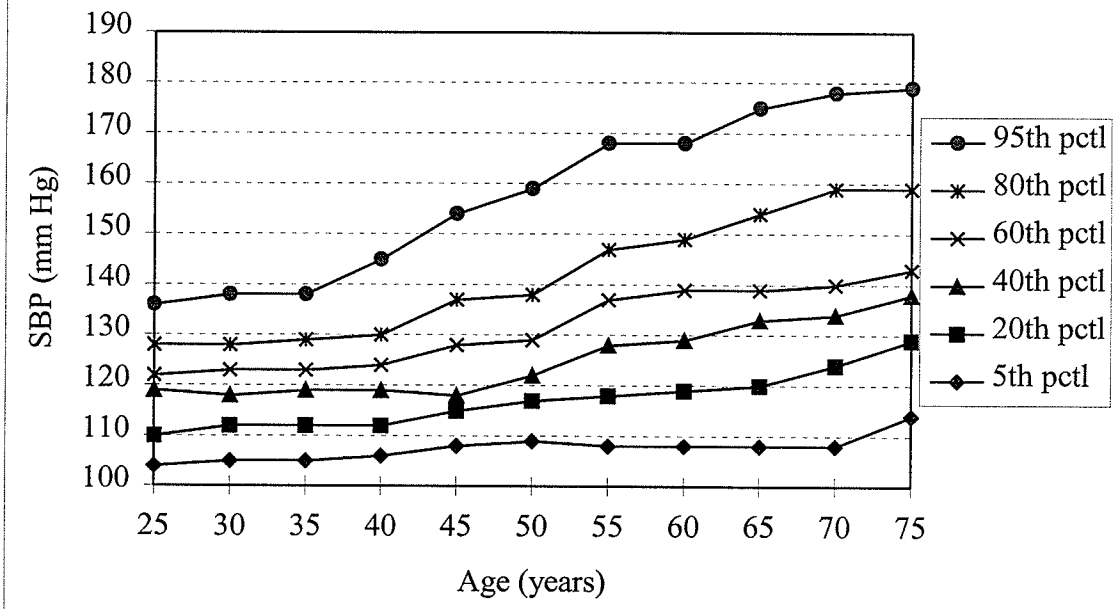
Table 6.2 Mean and standard deviation of Systolic Blood Pressure, Diastolic Blood Pressure and Body Mass Index in subjects free of Ischemic Heart Disease, by age.

Age (years)	SBP (mm Hg)	DBP (mm Hg)	BMI (kg/m^2)
25	120.9 ± 10.4	74.4 ± 8.0	22.7 ± 2.4
30	121.2 ± 10.7	75.6 ± 8.0	23.8 ± 2.6
35	122.1 ± 11.1	76.8 ± 8.4	24.6 ± 2.6
40	123.6 ± 12.1	78.3 ± 8.8	25.1 ± 2.6
45	126.1 ± 14.0	79.8 ± 9.5	25.4 ± 2.7
50	129.4 ± 16.1	81.2 ± 10.0	25.6 ± 2.8
55	132.7 ± 17.2	82.5 ± 10.2	25.6 ± 2.8
60	135.1 ± 18.0	82.6 ± 9.9	25.6 ± 3.1
65	138.6 ± 18.8	82.4 ± 9.9	25.6 ± 3.0
70	139.9 ± 19.1	81.2 ± 9.6	25.4 ± 3.0
75	141.0 ± 19.1	80.0 ± 9.5	24.7 ± 3.0

6.2.1 Percentile distribution of Systolic Blood Pressure

The percentile distribution of SBP with age is plotted in Figure 6.3. The increasing variability of SBP with age can be seen by the widening difference between the 5th and 95th percentile points of the SBP distribution. While the 5th percentile remained relatively stable with age, the 95th percentile began to increase at age 40 years. Up to age 40 years, the 5th and 95th percentiles spanned a range of 35 mm Hg while by age 55 years the range widened to 60 mm Hg.

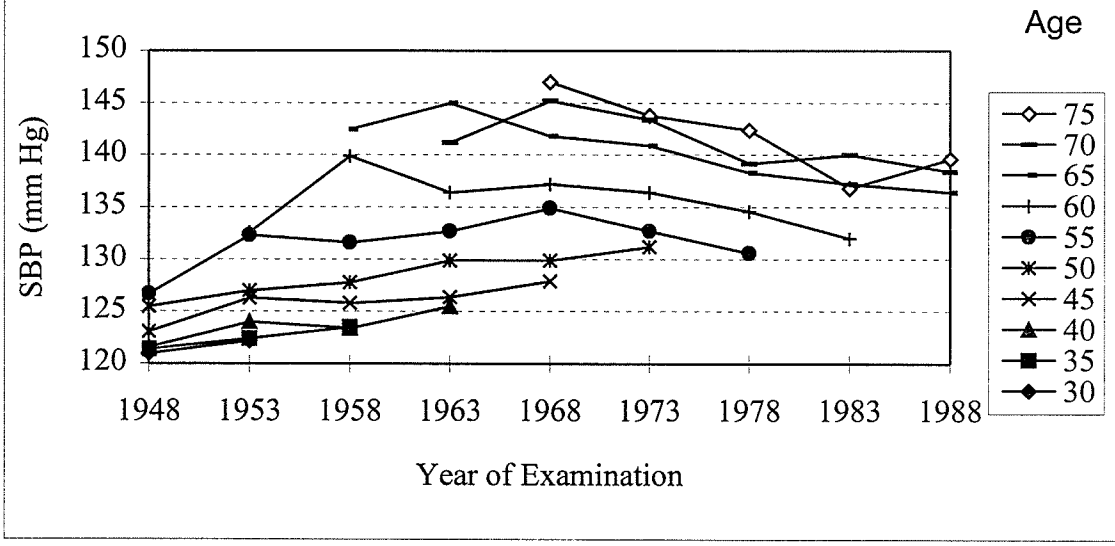
Figure 6.3: Percentiles of Systolic Blood Pressure distribution by age



6.2.2 Age and period effects on Systolic Blood Pressure

Secular effects on SBP can be seen in the plot of mean SBP by age and calendar period at examination as shown in Figure 6.4. Values joined by the same line are the SBP means of different subjects at the same age, but examined during different periods of time. In general, there was a tendency for mean SBP at each 5-year age to increase over calendar time, from entry to the study through the 1960s. For age categories where data is available both before and after that decade, there appeared to be a tendency for mean SBP to decline after the 1960s. This decline could be observed for men over age 55 years. This indication of changing mean SBP at different periods over time, suggests that calendar period, indicated by year of examination, will need to be considered as a potential influence in future modeling of effects of SBP.

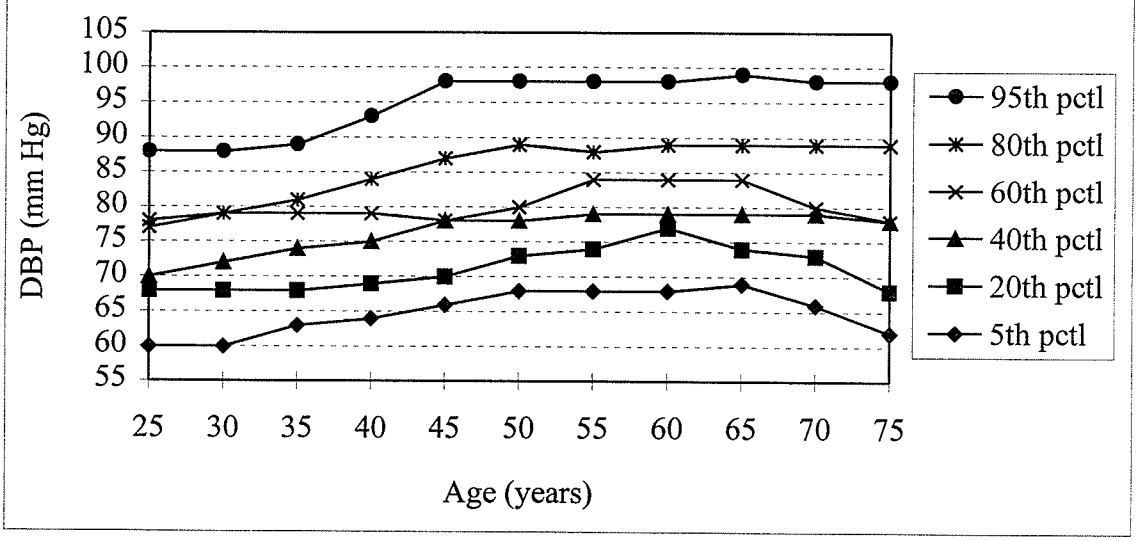
Figure 6.4: Age and period effects on Systolic Blood Pressure



6.2.3 Percentile distribution of Diastolic Blood Pressure

Age specific percentiles of DBP are plotted in Figure 6.5 and show a reasonably consistent pattern for the distribution of DBP with age. The range of values defining the middle 90% of subjects, i.e. between the 5th and 95th percentiles, was 35 to 40 mm Hg, for measurements up to age 60 years, and increased slightly after age 60 years.

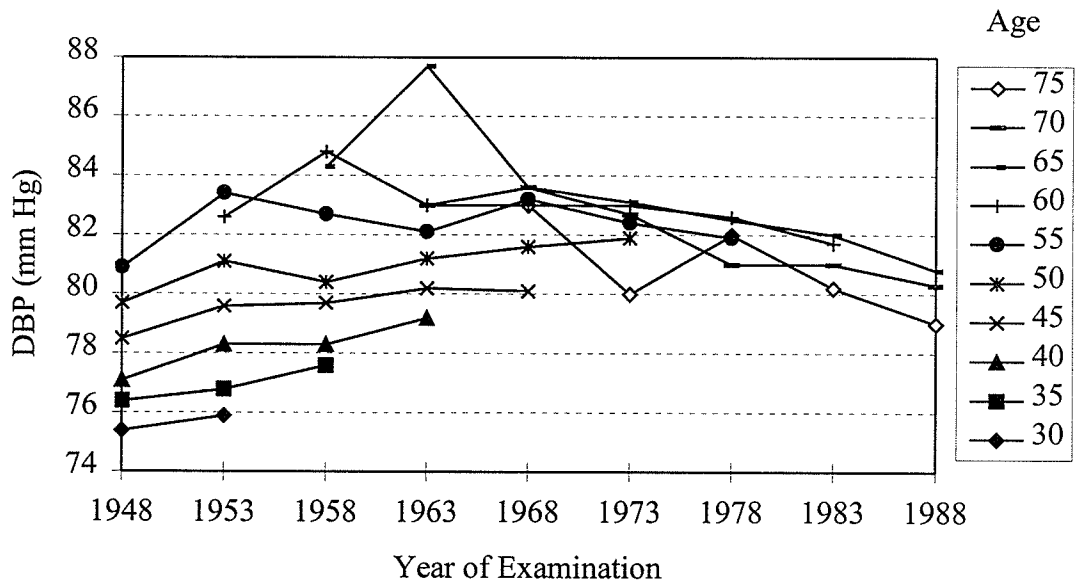
Figure 6.5: Percentiles of Diastolic Blood Pressure distribution by age



6.2.4 Age and period effects on Diastolic Blood Pressure

Mean DBP is plotted by age and calendar period as shown in Figure 6.6. Points joined by the same line are the mean DBP of different subjects at the same age examined in different periods of time. The tendency in the early years of the study for mean DBP to increase at all ages suggests secular effects. Over time, starting after the late 1960s for most ages, there was a decline in mean DBP for men of the same age. The pattern within age groups over time for DBP is similar to that previously described for SBP.

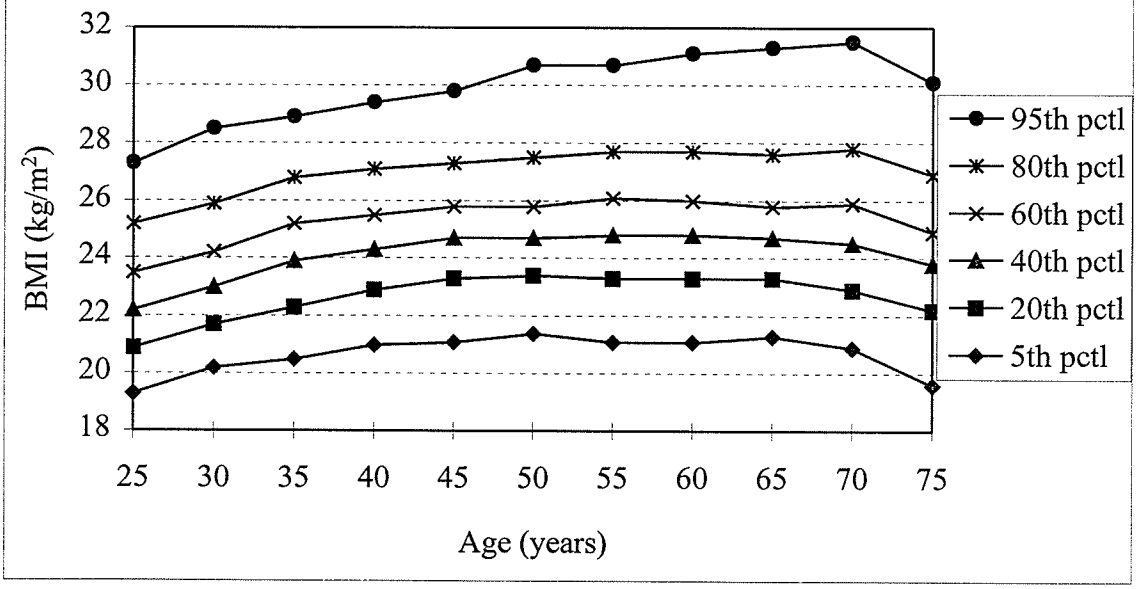
Figure 6.6: Age and period effects on Diastolic Blood Pressure



6.2.5 Percentile distribution of Body Mass Index

The percentiles of the BMI distribution were plotted as Figure 6.7. The percentiles of the BMI distribution maintained a consistent pattern with advancing age. The middle 60% of BMI values, as shown by the quintile lines of the 20th, 40th, 60th and 80th percentile, stayed parallel over the entire range of ages. The flattening of these quintile lines at age 50 years is consistent with the levelling off of the mean BMI at that age. The difference in BMI values between the 5th and 95th percentile changed very little with age, increasing from a difference of 8 kg/m^2 at age 25 years to just over 10 kg/m^2 by age 75 years.

Figure 6.7: Percentiles of Body Mass Index distribution by age



6.2.6 Age and period effects on Body Mass Index

There was a tendency for mean BMI, at all ages, to increase in the first five years of the study. Consistent trends in mean BMI over the 45-year period of time at specific ages were difficult to discern. Three distinct patterns of mean BMI over time were apparent when viewed separately for ages 30 to 45 years, ages 45 to 60 years and ages 60 through 75 years. The age and period effects for these three subsets are presented in Figure 6.8, Figure 6.9 and Figure 6.10 respectively. At ages 30 through 45 years, as seen on Figure 6.8, mean BMI increased with each 5-year age. As well, mean BMI progressively increased with calendar period at each of these ages. At ages 45 through 60 years, shown on Figure 6.9, mean BMI remained stable and virtually indistinguishable in value at all calendar periods. Mean BMI at age 45 years, recorded at examinations between 1948 and 1968, at age 50 between 1948 and 1973, at age 55 between 1948 and 1978 and at age 60 between 1953 and 1983 varied only by 0.4, 0.3, 0.5 and 0.7 kg/m^2 respectively. Consequently, at these ages there was no effect of time period of measurement, and further, mean BMI over this 15-year age range remained constant. From age 60 years, and older, mean BMI progressively declined, as shown in Figure 6.10. There was a period effect as evidenced by a tendency for mean BMI to be higher in men the same age in more recent years.

Figure 6.8: Age and period effects on Body Mass Index, ages 30 through 45 years

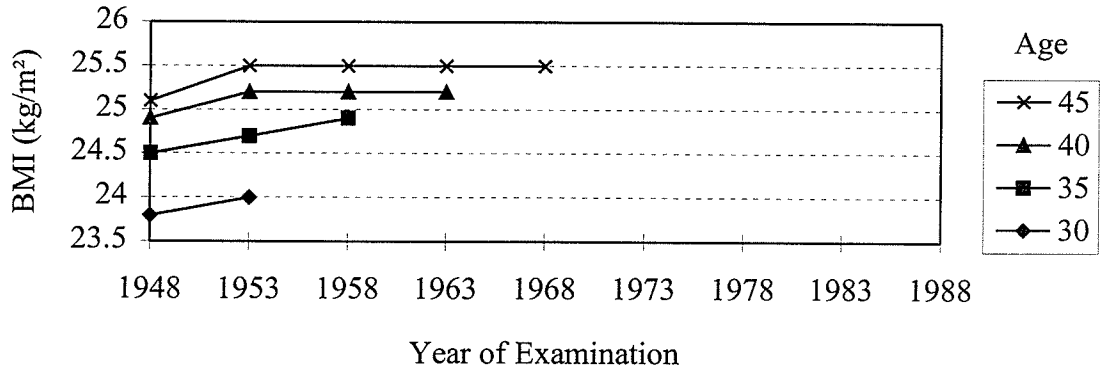


Figure 6.9: Age and period effects on Body Mass Index, ages 45 through 60 years

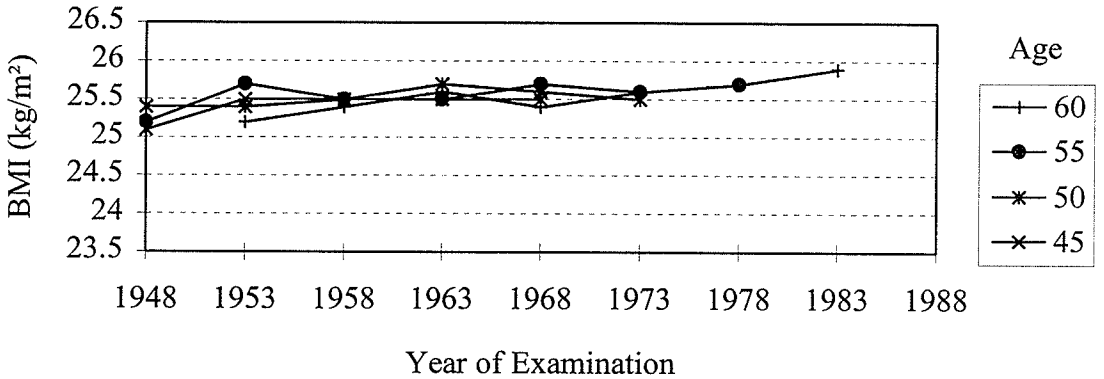
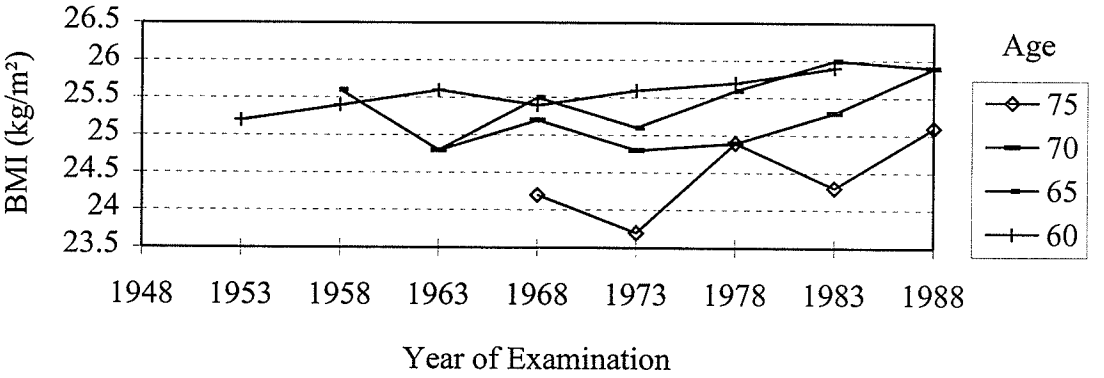


Figure 6.10: Age and period effects on Body Mass Index, ages 60 through 75 years



6.2.7 Prevalence of Diabetes Mellitus

There were no diabetics in this cohort at entry to the study. The point prevalence of DM was less than 1 percent before age 50 years, and increased to almost 9 percent by age 75 years, as shown in Table 6.3. The low prevalence before age 50 years suggests that almost all subjects with DM in this study would be classified as adult onset, Type II diabetics.

Table 6.3 Prevalence of Diabetes Mellitus and distribution of Smoking status in subjects free of Ischemic Heart Disease, by age.

Age (years)	Diabetes Mellitus (%)	Smoking Status (%)			
		Current smoker	Ex-smoker	Never smoked	Unknown
25	0	64	5	19	12
30	0	68	5	17	10
35	0	65	8	16	10
40	0.2	63	12	15	10
45	0.5	57	19	15	9
50	1.2	50	27	15	8
55	2.9	41	37	15	6
60	4.5	34	45	16	6
65	5.7	28	52	16	4
70	7.6	24	56	16	3
75	8.8	22	58	16	4

6.2.8 Prevalence of Smoking

As shown in Table 6.3, before age 50 years more than half of the MFUS members smoked. As the percentage of smokers decreased from 64 percent at age 25 years to 22 percent at age 75 years, the proportion of ex-smokers correspondingly increased. The proportion of study members who never smoked remained between 15 to 19 percent at all ages. Smoking information is missing for about 14 percent of subjects overall. The proportion with missing smoking information decreased from 12 percent at age 25 years to 4 percent by age 75 years.

6.2.9 Summary of risk factor profiles

The patterns observed in terms of SBP, DBP, BMI, DM and SM at 5-year age cross sections over the 45-year follow-up period have been described. The patterns exhibited for mean BP over time, both with SBP and DBP, are similar from younger ages. Increases with age were observed both in the mean and the standard deviation of BP measurements. A continuing increase in mean SBP was observed through to age 75 years, while mean DBP declined after age 60 years. Because the pattern of BP with age appears to depend, to some extent, on the period of time during which BP was recorded, it will be important to control for calendar period in subsequent analysis.

Following an initial increase in mean BMI from age 25 through 40 years of age, the mean BMI remained constant to about 60 years of age, and declined after that. The largest influence on the increase in the mean of the BMI distribution after age 40 years was the increased frequency of high BMI values. This can be seen through the increased

difference between the 80th and 95th percentiles of the BMI distribution with age. Patterns with BMI by age and time were best described in three age sub-groups. At both younger ages, age 40 years or less, and older ages, age 60 years or more, age and period effects were present. At age 40 through age 60 years, mean BMI was almost constant, unaffected by either age or period.

Prevalence of diabetes increased with age, from zero before age 50 years in this cohort. Smoking prevalence decreased with age.

6.3 Tracking of risk factors

Tracking of risk factors was examined for SBP, DBP and BMI using two methods. Pearson correlation coefficients were calculated for pairs of measurements at 5-year intervals up to 40 years apart for SBP, DBP and BMI. In addition, the relative likelihood of remaining in the top or bottom quintile of the distributions of SBP, DBP and BMI on repeated measurement was determined. The number of subjects contributing observations to the determination of these tracking indicators is presented in Table 6.4. All subjects who were examined at these ages had SBP and DBP recorded. On some occasions BMI was not recorded and hence the number of subjects with observations available for these calculations is fewer than the number of subjects with measurements for BP calculations. Missing BMI measurements were more frequent at older ages than at younger ages.

Table 6.4 Number of subjects with measurements at pairs of ages for the calculation of the Pearson correlation coefficient and the relative likelihood measure of tracking for Blood Pressure and Body Mass Index.

Age	30	35	40	45	50	55	60	65	70	75
25	288	308	305	296	275	257	230	181		
	286	302	300	283	250	230	191	129		
30		1669	1778	1737	1646	1531	1384	1087	767	
		1625	1730	1698	1548	1390	1163	820	569	
35			2710	2718	2580	2412	2165	1761	1275	368
			2617	2632	2435	2192	1849	1351	922	259
40				3222	3104	2894	2610	2130	1590	510
				3108	2924	2628	2241	1637	1158	369
45					3313	3110	2803	2308	1724	612
					3124	2836	2416	1778	1264	433
50						3177	2878	2358	1766	643
						2851	2457	1795	1275	453
55							2922	2397	1801	679
							2440	1796	1284	478
60								2405	1809	687
								1734	1240	482
65									1740	693
									1082	436
70										658
										397

At each pair of ages, the number in the first row is the number of subjects with pairs of blood pressure measurements and the number in the second row is the number of subjects with pairs of body mass index measurements.

6.3.1 Serial correlation of repeated measurements over time by age

6.3.1.1 Systolic Blood Pressure, correlation

The Pearson correlation coefficients for serial measurements of SBP between age 25 and 75 years are shown in the first row of each triplet at pairs of ages in Table 6.5. The correlation between pairs of SBP measurements were positive and, with the few exceptions as noted, statistically significant at the $p<0.01$ level. The correlation coefficients viewed diagonally from the top left to the bottom right in this table are the same time interval apart between different ages. As viewed from the top row along a diagonal, the magnitude of the correlation coefficient increased for pairs of measurements from younger ages to a maximum correlation of 0.50 for pairs of measurements 5 years apart between age 45 and 50 years, 0.40 for measurements 10 years apart, 0.32 for measurements 15 years and 0.31 for measurements 20 years apart. This suggests that the correlation between SBP measurements, from the same age, decreased with increasing length of time between measurements.

6.3.1.2 Diastolic Blood Pressure, correlation

The Pearson correlation coefficients for serial measurements of DBP recorded between age 25 and 75 years of age are shown in the second row of each triplet at pairs of ages in Table 6.5. The correlation between pairs of DBP measurements were positive and, with the few exceptions as noted, statistically significant at the $p<0.01$ level. The magnitude of the correlation coefficient the same time interval apart increased for pairs at younger ages, where at least one measurement was recorded before age 50 years. The

strongest correlation was found for measurements at middle ages, with all correlation coefficients, five years apart, between ages 40 and 60 years, being at least 0.40. Ten-year correlation coefficients at these ages ranged between 0.31 and 0.35. The 15-year or 20-year correlation coefficients for DBP measurements in general ranged between 0.20 and 0.30. Thus, the correlation between DBP measurements from the same age decreased with increasing length of time between measurements.

6.3.1.3 Body Mass Index, correlation

Serial BMI measurement had high correlation as shown in the last row of each triplet at pairs of ages in Table 6.5. All pairs of BMI measurements examined up to 35 years apart, had correlation coefficients at least as large as 0.52. At intervals of 5, 10 and 15 years, at all ages between 30 and 75 years correlation coefficients ranged between 0.71 and 0.88. Similar to the trends found with BP correlation coefficients, BMI correlation coefficients decreased with increasing interval of time between measurements. Correlation coefficients for BMI increased with age for measurements the same interval of time apart for pairs of measurements up to age 60 years.

Table 6.5 Pearson correlation coefficients for serial measurements of Systolic Blood Pressure, Diastolic Blood Pressure and Body Mass Index.

Age	30	35	40	45	50	55	60	65	70	75
25 S	.35	.26	.29	.27	.18	.23	.16*	.18*		
D	.08*	.21	.25	.21	.20	.15	.09	.15		
B	.79	.74	.62	.60	.58	.57	.53	.52		
30 S		.35	.34	.32	.31	.30	.23	.23	.14	
D		.30	.26	.25	.26	.23	.18	.15	.18	
B		.85	.78	.73	.68	.62	.61	.57	.47	
35 S			.37	.33	.28	.26	.17	.17	.18	.12*
D			.35	.30	.30	.26	.18	.17	.21	.05*
B			.85	.79	.73	.68	.64	.60	.52	.41
40 S				.45	.40	.32	.26	.24	.20	.11*
D				.40	.35	.30	.21	.19	.15	.01*
B				.86	.81	.76	.71	.67	.60	.54
45 S					.50	.40	.32	.27	.24	.15
D					.46	.34	.30	.24	.18	.13
B					.87	.81	.76	.72	.67	.60
50 S						.49	.40	.32	.27	.24
D						.43	.33	.25	.22	.21
B						.86	.81	.79	.73	.64
55 S							.49	.36	.33	.26
D							.44	.31	.28	.22
B							.87	.82	.77	.71
60 S								.46	.37	.27
D								.40	.32	.20
B								.88	.80	.71
65 S									.44	.36
D									.37	.27
B									.86	.79
70 S										.42
D										.26
B										.87

At each age, the first row (denoted S) is the correlation coefficient for pairs of systolic blood pressure measurements, the second row (denoted D) for diastolic blood pressure measurements and the third row (denoted B) for body mass index measurements. All correlation coefficients are statistically significant at $p<0.01$ unless noted by *.

6.3.1.4 Summary of correlation between measurements by age

In general, similar patterns across age and time intervals were found for the correlation of SBP measurements and for the correlation of DBP measurements. With few exceptions, the correlation coefficients were greater for SBP than for DBP measurements at the same ages. Comparison of SBP and DBP correlation coefficients from the same age and with the same time interval between measurements showed that for both BP measurements correlation was the strongest when measured at ages between 40 and 60 years. SBP measurements at 5-year intervals at ages between 40 and 55 years were in the range of 0.45 to 0.50, while for DBP they were 0.40 to 0.46. In general, the same pattern for decreasing correlation with increasing interval of time between measurements was evident for both SBP and DBP. Correlation of BMI 5 years or 10 years apart was affected very little by age at examination. Between age 30 and 75 years, all 5-year correlation coefficients for BMI ranged from 0.85 to 0.88, and 10-year correlation coefficients from 0.78 to 0.82. The correlation for pairs of BMI measurements at 15, 20, 25 or 30 years between ages 30 through 75 years were all at least 0.60 in magnitude. In all instances, the correlation between pairs of BMI measurements was greater than the correlation for either BP measurement.

6.3.2 Relative likelihood methods for tracking

6.3.2.1 Tracking in the top quintile

The relative likelihood of tracking for subjects in the top quintile of the SBP, DBP and BMI distributions is shown in Table 6.6. Each number in this table corresponding to

a pair of ages is a ratio of proportions. This ratio, called the relative likelihood, is the proportion of subjects in the top quintile at the younger age who remained in the top quintile at the older age, divided by the proportion of all subjects with examinations at both ages who were in the top quintile at the older age. For example, between age 25 and 30, 47.8% of the subjects in the top SBP quintile at age 25 remained in the top SBP quintile at age 30 years, while 24.0% of all subjects with measurements at both ages were in the top SBP quintile at age 30 years. Hence, the likelihood of remaining in the top SBP quintile from age 25 to age 30 years was 47.8/24.0=1.99 times greater than the overall likelihood of being in the top SBP quintile at age 30 years. Cutpoints defining BP quintiles that would identify exactly 20% of subjects is highly unlikely, due to the inherent digit preference in recording of BP values. However, this is not a problem with the calculation of the relative likelihood statistic, because the same cutpoint of the BP distribution at the older age is used for both the numerator and denominator.

After age 40 years, subjects in the top quintile of the SBP distribution were more than twice as likely to remain in the top quintile 5 years later than others were to be in the top quintile. This can be seen by the number in the top row of the triplet ranging from 2.15 to 2.46 along the first diagonal of Table 6.6 at these ages. The strongest evidence for SBP tracking was found for measurements at pairs of ages from 40 through to 55 years.

The relative likelihood of tracking for subjects in the top quintile of the DBP distribution are slightly lower than the relative likelihood tracking measures for SBP, at

comparable ages and over comparable intervals of time. The largest relative likelihoods were found for measurements at 5-year intervals between ages 40 to 55 years, when at all pairs of these ages, subjects in the top DBP quintile were more than twice as likely as others to be in the top quintile for the next 5 years.

The relative likelihood of staying in the top quintile of the BMI distribution over a five year interval increased in magnitude from 3.41 times at ages 25 to 30 to 4.59 times by ages 70 to 75 years. After age 30 years, the relative likelihood of a subject in the top quintile of the BMI distribution to remain in the top quintile, was at least 3 fold for measurements up to 20 years apart. Every relative likelihood tracking coefficient in the top quintile for BMI was considerably greater than the corresponding coefficient for either SBP or DBP at the same pair of ages.

Table 6.6 Relative likelihood of remaining in the top quintile of the Systolic Blood Pressure, Diastolic Blood Pressure or Body Mass Index distributions on repeated measurements.

Age	30	35	40	45	50	55	60	65	70	75
25 S	1.99	1.34*	1.63	1.81	1.62					
D	1.10*	1.34	1.37*	1.32*	1.46					
B	3.41	3.30	2.63	2.54	3.04					
30 S		1.64	1.87	1.86	1.62	1.70				
D		1.26	1.39	1.44	1.39	1.34				
B		3.39	3.34	3.02	2.92	2.74				
35 S			1.69	1.80	1.58	1.73	1.28			
D			1.57	1.60	1.53	1.52	1.37			
B			3.58	3.26	3.18	3.06	2.91			
40 S				2.34	1.98	1.87	1.51	1.57		
D				2.22	2.20	1.76	1.50	1.43		
B				3.57	3.40	3.26	3.12	2.96		
45 S					2.40	2.42	2.00	1.71	1.57	
D					2.35	1.92	1.89	1.68	1.38	
B					3.58	3.41	3.14	3.17	2.95	
50 S						2.43	2.03	1.78	1.57	1.48
D						2.20	1.83	1.55	1.49	1.41*
B						3.60	3.46	3.35	3.14	2.68
55 S							2.46	2.12	2.12	1.85
D							1.99	1.68	1.56	1.49
B							3.75	3.63	3.35	3.19
60 S								2.20	1.72	1.76
D								1.92	1.56	1.41
B								3.78	3.51	3.16
65 S									2.15	1.74
D									1.89	1.65
B									3.97	3.84
70 S										2.33
D										1.78
B										4.59

At each age, row S is the relative likelihood for pairs of SBP measurements, row D for DBP measurements and row B for BMI measurements. All relative likelihood measures are statistically significant at $p<0.01$ unless noted by *.

6.3.2.2 Tracking in the bottom quintile

The relative likelihood of tracking for subjects in the bottom quintile is shown in Table 6.7. For SBP, subjects after age 35 years were at least one and a half times more likely to remain in the lowest quintile than were others to be in the lowest quintile for measurements at intervals up to 25 years apart. Hence, there is evidence for SBP tracking, both in the top quintile and the bottom quintile of the distribution.

The tracking coefficients for DBP measurements in the bottom quintile show that at ages after 30 years over intervals up to 15 years, subjects were at least one and a half times more likely to remain in the lowest quintile than were others to be in the lowest quintile.

Significant evidence for tracking in the bottom quintile of the BMI distribution was also found. BMI tracking in the bottom quintile was stronger than that for blood pressure at comparable ages, with relative likelihood coefficients greater than 3 fold for measurements 5 or 10 years apart, at all ages between 30 and 65 years. Tracking coefficients were greater for those pairs of measurements closer together in time and tended to be fairly consistent in magnitude between ages 40 and 65 years.

Table 6.7 Relative likelihood of remaining in the bottom quintile of the Systolic Blood Pressure, Diastolic Blood Pressure and Body Mass Index distributions on repeated measurements.

Age	30	35	40	45	50	55	60	65	70	75
25 S	1.47*	2.00	2.01	1.56*	1.26*					
D	1.24*	2.08	1.30*	1.69*	1.18*					
B	3.51	3.32	2.98	2.57	2.54					
30 S		1.74	1.82	1.70	1.63	1.62				
D		1.81	1.80	1.52	1.16*	1.43				
B		3.62	3.39	2.96	2.63	2.47				
35 S			1.86	1.54	1.53	1.56	1.54			
D			2.52	1.83	1.56	1.57	1.34			
B			3.78	3.33	2.98	2.67	2.57			
40 S				1.81	1.73	1.70	1.49	1.51		
D				2.16	1.61	1.73	1.37	1.71		
B				3.70	3.36	3.01	2.84	2.56		
45 S					1.84	1.82	1.55	1.48	1.46	
D					1.78	1.57	1.72	1.64	1.37	
B					3.67	3.25	3.07	2.92	2.72	
50 S						2.08	1.96	1.59	1.30	1.57
D						1.78	1.56	1.54	1.46	1.25*
B						3.62	3.28	3.11	2.92	2.38
55 S							2.49	1.92	1.54	1.54
D							1.90	1.55	1.61	1.59
B							3.51	3.46	3.09	2.48
60 S								2.07	1.77	2.03
D								1.98	1.65	1.69
B								3.70	3.26	2.59
65 S									2.13	1.71
D									2.10	1.40*
B									3.61	2.76
70 S										2.06
D										1.88
B										3.14

At each age, row S is the relative likelihood for pairs of SBP measurements, row D for DBP measurements and row B for BMI measurements. All relative likelihood measures are statistically significant at $p<0.01$ unless noted by *.

6.3.3 Summary of evidence for tracking

Tracking of the continuous risk factors, SBP, DBP and BMI, was examined using two statistical approaches, correlation analysis and the calculation of the relative likelihood. The correlation coefficient measures the strength of the linear relationship between two variables across their entire range of values. The relative likelihood approach is a measure of the tendency for individuals on repeated measurement to remain in the top, or bottom, part of the distribution of measurements.

Correlation analysis showed coefficients to be greatest for pairs of measurements at age 40, 45, 50 and 55 years of age. Coefficients were greater for shorter intervals of time between measurements, and decreased with longer intervals between measurements. In general, correlation coefficients were greatest for BMI and greater for SBP than for DBP at the same pair of ages.

The relative likelihood measure was used to assess the magnitude of tracking in the top and bottom quintiles of the distributions for SBP, DBP and BMI. The relative likelihood was of similar magnitude for SBP and DBP and was greater for BMI measurements than with either BP at every pair of ages. For the same pair of ages between 40 and 55 years, over intervals of 5, 10 and 15 years, the relative likelihood of tracking in the top quintile was typically greater than the relative likelihood of tracking in the bottom quintile for both SBP and DBP. At ages under 40 years, for BP, tracking in the bottom quintile was typically greater than tracking in the top quintile over 5 and 10

year intervals. BMI tracking was greater in the top compared to the bottom quintile at older ages, and greater in the bottom compared to the top quintile at younger ages.

6.4 Effect of aging on the relationship between risk factors and incidence of Ischemic Heart Disease

6.4.1 Risk factors and patterns of incidence of Ischemic Heart Disease

Subjects were classified within quintiles of the distributions of SBP, DBP and BMI, as diabetic or non-diabetic, and within smoking categories at selected ages between 30 and 75 years. The incidence of IHD per 1,000 pyrs from each age was calculated for subjects within these categories to explore the relationship between these risk factors at specific ages and the incidence of IHD. For each risk factor, the incidence of IHD was plotted and the pattern in incidence across categories at each age was described. The incidence ratio was calculated as the incidence of IHD for those in the elevated risk category divided by the incidence of IHD for those in the lowest risk category. The incidence difference was calculated as the difference in incidence of IHD between subjects in the highest and lowest risk categories. The highest and lowest risk categories were defined as the top and bottom quintile, respectively, of the SBP, DBP or BMI distributions, diabetics and non-diabetics, and current smokers compared to never smokers. No statistical tests of the incidence of IHD across categories of each risk factor along with the IR and the ID were calculated. Patterns were described at different ages to

assess the effect aging may have on the relationship of each risk factor with incidence of IHD.

Increasing incidence of IHD with increasing SBP quintiles are apparent as shown in Figure 6.11. Although incidence of IHD in the bottom quintile, labeled Q1, was always lower than the incidence in Q2, and the incidence of IHD in the top quintile, labeled Q5, was always greater than the incidence in Q4, the gradient across all five quintiles was monotonic only at ages 40 and 55 years. A trend of increasing incidence of IHD with increasing SBP quintiles, however, was apparent at all ages. The IR of 1.46 at age 30 years, as shown in Table 6.8, means that the incidence of IHD for the subjects in the top SBP quintile is 46% greater than the incidence of IHD for subjects in the lowest SBP quintile at this age. The IR ranged from a low of 1.41 at age 35 years to a high of 2.07 at age 75 years. There was no consistent pattern of increasing, or decreasing, IR with age. At the same time the ID increased with age. The difference of incidence of IHD of 2.5 cases per 1,000 pyrs between those in the top and bottom SBP quintiles at age 30, increased to a difference of about 9 cases per 1,000 pyrs at ages 55 through 70 years. The increasing ID with age is apparent from the gradient across the five quintile categories becoming steeper with increasing with age, as shown in Figure 6.11.

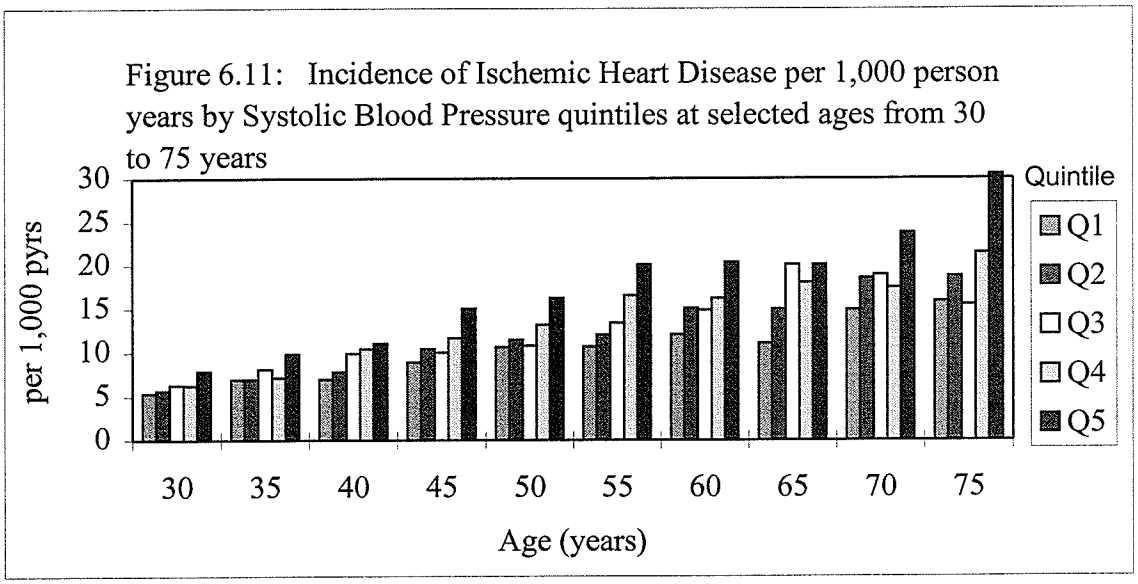


Table 6.8 Incidence ratio and incidence difference of Ischemic Heart Disease for men in the top quintile and in the bottom quintile of the Systolic Blood Pressure distribution by age

Age	30	35	40	45	50	55	60	65	70	75
Incidence Ratio	1.46	1.41	1.58	1.69	1.53	1.88	1.68	1.81	1.60	2.07
Incidence Difference IHD/1000 pyrs)	2.50	2.90	4.06	6.12	5.63	9.42	8.26	8.99	8.89	17.0

Gradients of IHD across DBP quintiles, shown in Figure 6.12, are similar to those described for SBP quintiles and incidence of IHD. The IR ranged from a low of 1.28 to a high of 1.80 between age 30 and 75 years, as shown in Table 6.9. There was no consistent trend in the magnitude of the IR with age. The ID between those in the top and

bottom quintiles generally increased with age, except for the slight decrease between age 40 and 45 years, and the more apparent decrease from age 55 to 60 years.

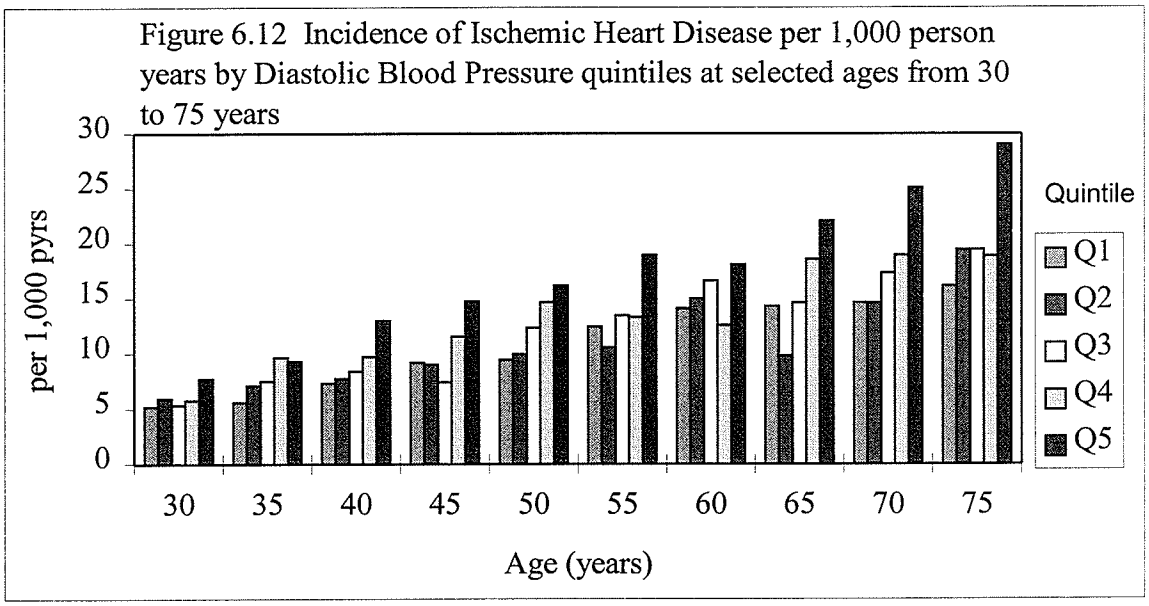


Table 6.9 Incidence ratio and incidence difference of Ischemic Heart Disease for men in the top quintile and in the bottom quintile of the Diastolic Blood Pressure distribution by age

Age	30	35	40	45	50	55	60	65	70	75
Incidence Ratio	1.49	1.66	1.77	1.60	1.71	1.52	1.28	1.54	1.72	1.80
Incidence Difference (IHD/1000 pyrs)	2.54	3.72	5.68	5.54	6.70	6.49	3.98	7.76	10.5	12.9

Overall, a trend for increasing incidence of IHD was found within quintiles of BMI at ages up to 70 years, as shown in Figure 6.13. The ID and the IR for IHD between the top and bottom quintile of the BMI distribution at each age was less than that for

either SBP (except at age 40 and 45 years) or DBP, as shown in Table 6.10. No consistent pattern was apparent with either the IR or ID and age.

Figure 6.13: Incidence of Ischemic Heart Disease per 1,000 person years by Body Mass Index quintiles at selected ages from 30 to 75 years

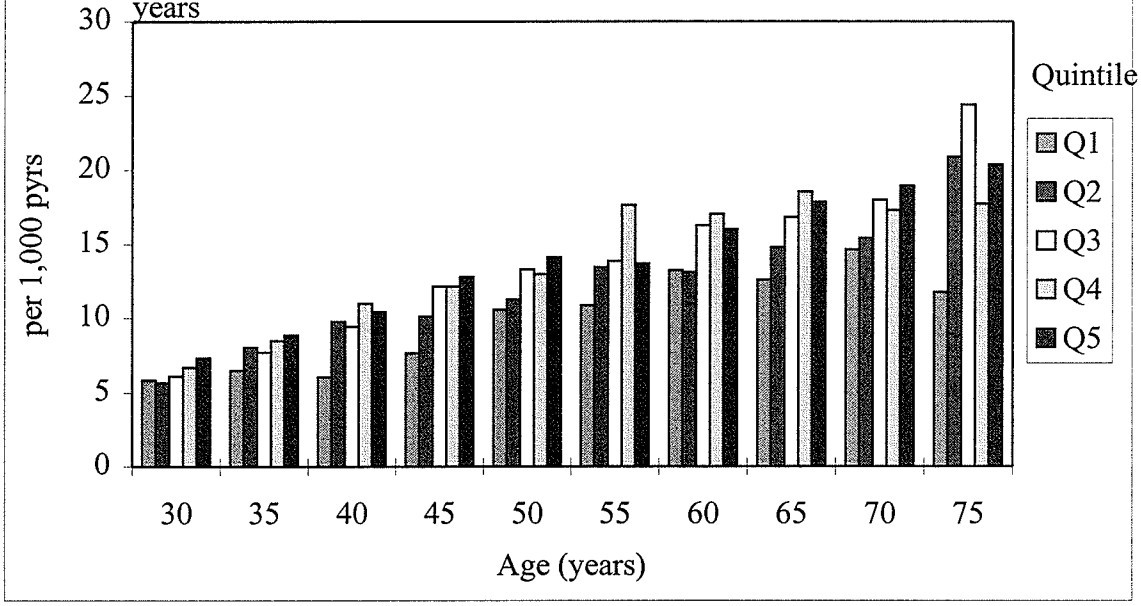


Table 6.10 Incidence ratio and incidence difference of incidence of Ischemic Heart Disease for men in the top quintile and in the bottom quintile of the Body Mass Index distribution by age.

Age	30	35	40	45	50	55	60	65	70	75
Incidence Ratio	1.26	1.36	1.72	1.67	1.34	1.26	1.21	1.42	1.29	1.73
Incidence Difference (IHD/1000 pyrs)	1.50	2.34	4.35	5.12	3.55	2.82	2.78	5.25	4.30	8.62

The largest IR and ID for presence of diabetes were found among subjects at ages 50, 55, 60 and 65 years, as shown in Figure 6.14. An IR of almost 2 fold (1.93 at age 55 years) or greater, as shown in Table 6.11, and a difference in IHD incidence of at least 13 cases per 1,000 pyrs for diabetic compared to non-diabetic subjects were found. After age 65 years, a much smaller effect of diabetes both in IR and ID were found where at age 75 years IHD incidence was almost identical in diabetic and non-diabetic men.

Figure 6.14: Incidence of Ischemic Heart Disease per 1,000 person years for Diabetic and Non Diabetic men at selected ages from 30 to 75 years

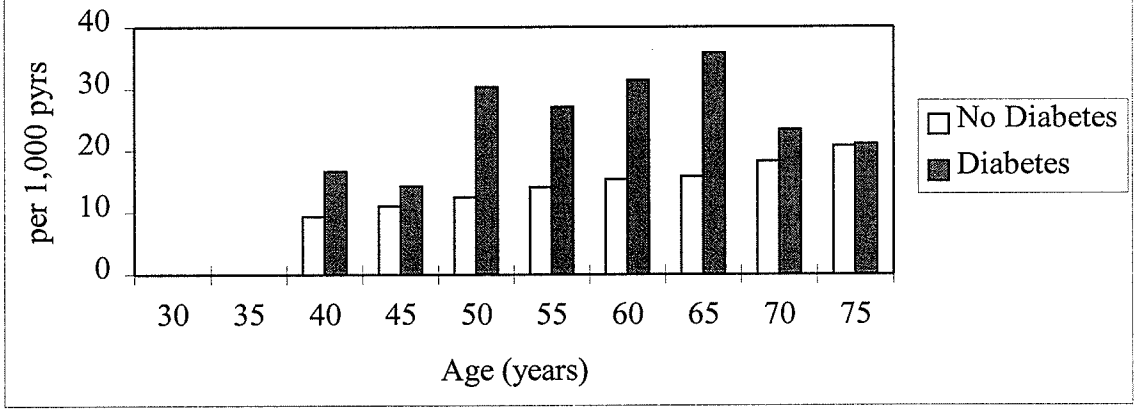


Table 6.11 Incidence ratio and incidence difference of Ischemic Heart Disease for Diabetic and Non Diabetic men by age.

Age	30	35	40	45	50	55	60	65	70	75
Incidence Ratio	-	-	1.78	1.29	2.43	1.93	2.05	2.27	1.28	1.01
Incidence Difference (IHD/1000 pyrs)	-	-	7.27	3.20	17.9	13.0	16.1	20.0	5.13	0.31

Up to age 60 years, current smokers consistently had higher incidence of IHD than former smokers, who in turn had higher incidence of IHD than those who never smoked, as shown in Figure 6.15. While the difference in incidence of IHD between current smokers and never smokers increased to age 55 years, the IR decreased, as shown in Table 6.12. After age 60 years, a difference in incidence of IHD between current smokers and non-smokers was less evident. The IR and ID decreased at age 60 and again at age 65 years. After age 65 years, incidence of IHD among current smokers was lower than the incidence among those who had quit smoking or had never smoked. At age 70 and 75 years, the incidence of IHD in current or former smokers was less than that among non smokers.

Figure 6.15: Incidence of Ischemic Heart Disease per 1,000 person years by Smoking Status at selected ages from 30 to 75 years

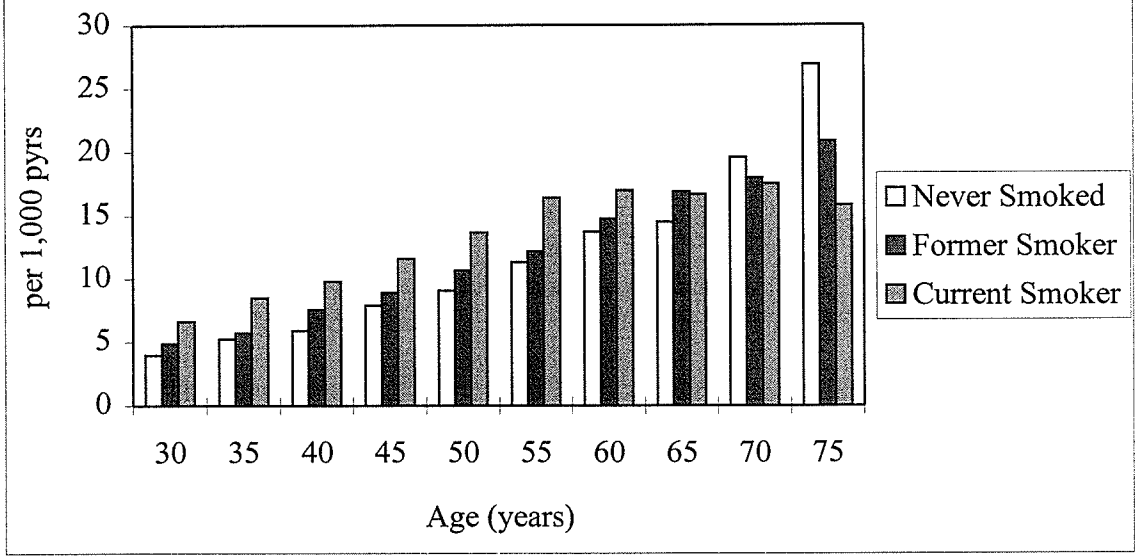


Table 6.12 Incidence ratio and incidence difference of Ischemic Heart Disease for Current Smokers and Never Smokers by age.

Age	30	35	40	45	50	55	60	65	70	75
Incidence Ratio	1.66	1.62	1.66	1.47	1.50	1.44	1.24	1.15	0.89	0.59
Incidence Difference (per1000 pyrs)	2.64	3.24	3.89	3.72	4.61	5.05	3.24	2.18	-2.1	-11.

6.4.1.1 Summary of risk factors and patterns of incidence of Ischemic Heart Disease

Patterns of incidence of IHD across categories of risk factors were described, stratified by age. Incidence of IHD was shown to increase across SBP and DBP quintiles at each age up to 70 years. The difference in incidence of IHD from the top to the bottom quintile of BP as measured by the ID increased with age. No consistent trend with IR was found with either BP. A trend of increasing incidence of IHD with increasing BMI quintile was apparent for most ages, however, the magnitude of the ID and IR were in general smaller for BMI compared to either SBP or DBP. The IR and ID comparing diabetics to non-diabetics were greatest at ages between 50 and 65 years. The IR for current smokers compared to never smokers tended to decrease with age, while the ID generally increased from age 30 years to age 55 years, and declined thereafter. At age 70 and 75 years, incidence of IHD was lower among current or former smokers in comparison to those who never smoked.

6.4.2 Risk factors and patterns of incidence of Angina Pectoris, Myocardial Infarction and Sudden Death

Because IHD manifests as one of three different types, a different mechanism for each disease manifestation would be implied if relationships of a risk factor varied with IHD type. It is therefore important to determine whether the relationships between the risk factors and IHD manifestations vary. To explore this, the incidence of AP, MI and SD from selected ages between 30 and 75 years was calculated for subjects in age-specific quintiles of SBP, DBP and BMI, for diabetic and non-diabetic men, and within smoking categories. Different gradients would reflect the impact aging might have on the relationship between these risk factors and each manifestation of IHD.

Incidence of AP, MI and SD across quintiles and within the categories of the risk factors were plotted. The age-specific IRs and IDs comparing incidence of each manifestation of IHD within the top and bottom quintiles for the SBP, DBP and BMI distributions are presented in Table 6.13. The IRs and IDs for categories of diabetes and smoking are presented in Table 6.14. The IRs are directly comparable between IHD and each IHD manifestation because the IR is a unitless measure of the relative incidence between the subjects in two categories of a risk factor. The magnitude of the IDs are not comparable among different manifestations of disease. However, it can be noted that the ID for AP, MI and SD sum to the ID for IHD at each age, in each risk factor category.

The IR for SBP at every age was greater for SD, than for either AP or MI as shown in Table 6.13. The IRs suggests that high SBP could be an important factor for SD at all ages, and a more important risk factor for AP than for MI from age 50 years

onward. A striking feature of the incidence of SD across SBP quintiles was the magnitude of the incidence in the top quintile compared to the other four quintiles at ages 40 through 60 years. At these ages SD incidence changed little across the first four quintiles, and increased for those in the top quintile.

Incidence of SD across DBP quintiles at ages 30, 35 and 40 showed inconsistent gradients, even though the IR for SD at age 30 and age 40 was greater than that for AP or MI. This suggests that men with DBP in the top quintile at younger ages are at a risk of SD greater than the men at any of the other four quintiles. At age 45 years and older, the IR for AP was consistently higher than that for MI or SD. Gradients with MI incidence were most apparent at age 65 and 70 years. From age 35 years and older, the greatest incidence of SD was consistently found for subjects in the highest DBP quintile, although there was no consistent gradient across the other four DBP quintiles.

The IR for BMI was greater for SD, than for either AP or MI at every age up to 50 years, with all IRs for SD greater than 2 up to age 45 years. From age 55 through age 70 years, the IR for BMI was greatest for AP, compared to the IR for either MI or SD.

Table 6.13 Incidence ratio and incidence difference of Ischemic Heart Disease, Angina Pectoris, Myocardial Infarction and Sudden Death for subjects in the top quintile compared to the bottom quintile of the Systolic Blood Pressure, Diastolic Blood Pressure and Body Mass Index distributions by age.

Risk factor	IHD type	Age	30	35	40	45	50	55	60	65	70	75
SBP	All	IR	1.46	1.41	1.58	1.69	1.53	1.88	1.68	1.81	1.60	2.07
		ID	2.50	2.90	4.06	6.12	5.63	9.42	8.26	8.99	8.89	17.0
	AP	IR	1.24	1.37	1.64	1.41	1.49	2.05	2.13	1.83	1.79	1.47
		ID	0.55	1.09	4.64	1.77	2.09	4.37	4.13	3.68	3.25	3.34
	MI	IR	1.42	1.41	1.39	1.69	1.45	1.68	1.30	1.62	1.28	2.94
		ID	1.16	1.33	1.44	2.54	2.19	3.48	2.27	3.42	2.69	13.7
	SD	IR	3.72	1.59	2.28	2.89	1.86	2.08	2.95	2.69	3.84	0.98
		ID	0.79	0.48	0.97	1.80	1.34	1.58	1.87	1.88	2.93	-0.0
DBP	All	IR	1.49	1.66	1.77	1.60	1.71	1.52	1.28	1.54	1.72	1.80
		ID	2.54	3.72	5.68	5.54	6.70	6.49	3.98	7.76	10.5	12.9
	AP	IR	1.25	1.57	1.48	1.91	2.31	1.80	1.87	1.74	1.14	0.63
		ID	0.65	1.35	1.53	2.96	3.96	3.59	3.72	3.77	0.91	-1.8
	MI	IR	1.49	1.80	1.81	1.52	1.37	1.39	0.94	1.50	1.93	1.66
		ID	1.11	2.02	2.78	2.20	1.81	2.31	-0.5	3.39	7.15	6.43
	SD	IR	2.97	1.50	3.04	1.22	1.59	1.28	1.41	1.25	4.48	1.00
		ID	0.77	0.35	1.37	0.37	0.94	0.59	0.76	0.60	2.44	-0.0
BMI	All	IR	1.26	1.36	1.72	1.67	1.34	1.26	1.21	1.42	1.29	1.73
		ID	1.50	2.34	4.35	5.12	3.55	2.82	2.78	5.25	4.30	8.62
	AP	IR	1.70	1.35	1.72	1.53	1.55	1.67	1.69	2.31	1.54	1.15
		ID	1.34	0.88	1.86	1.88	2.20	2.52	3.11	4.22	2.12	0.30
	MI	IR	0.89	1.19	1.53	1.47	1.05	1.00	1.00	1.07	1.35	2.02
		ID	-0.4	0.68	1.55	1.70	0.26	0.02	-0.0	0.55	2.73	8.01
	SD	IR	2.08	2.61	2.67	3.89	1.83	1.23	0.85	1.29	0.81	1.15
		ID	0.54	0.79	0.95	1.56	1.09	0.29	-0.3	0.47	-0.5	0.30

IR - incidence ratio; ID - incidence difference (events/1000 pyrs)

As shown in Table 6.14 at ages 50 though 65 years, incidence of AP and MI were greater for diabetics compared to non-diabetics, while incidence was similar after age 65 years. With SD, the IR remained consistently highest after age 50 years. The IR for smokers compared to non-smokers was consistently lowest for AP, intermediate for MI (except at age 35 years) and highest for SD up to age 60 years. At ages 60, 65 and 70 years, incidence of AP in smokers was similar to or slightly lower than the incidence of AP in non-smokers. This was also found for MI incidence at age 65 years and older.

Table 6.14 Incidence ratio and incidence difference of Ischemic Heart Disease, Angina Pectoris, Myocardial Infarction and Sudden Death for Diabetics versus non-Diabetics and Current Smokers versus Never Smokers by age.

Risk factor	IHD type	Age	30	35	40	45	50	55	60	65	70	75
DM	All	IR	-	-	1.78	1.29	2.43	1.93	2.05	2.27	1.28	1.01
		ID	-	-	7.27	3.20	17.9	13.0	16.1	20.0	5.13	0.31
	AP	IR	-	-	-	1.02	2.59	1.47	1.91	1.46	1.33	0.66
		ID	-	-	-	0.1	8.28	2.88	6.01	3.07	2.23	-2.7
	MI	IR	-	-	-	0.92	2.36	1.94	2.07	2.66	1.14	1.48
		ID	-	-	-	-0.4	7.79	5.83	7.44	12.2	1.34	-5.8
	SD	IR	-	-	-	3.77	2.16	3.56	2.41	3.72	1.76	6.08
		ID	-	-	-	3.49	1.81	4.33	2.63	4.76	1.56	8.78
SM	All	IR	1.66	1.62	1.66	1.47	1.50	1.44	1.24	1.15	0.89	0.59
		ID	2.64	3.24	3.89	3.72	4.61	5.05	3.24	2.18	-2.1	-11.
	AP	IR	1.32	1.48	1.53	1.27	1.29	1.30	0.96	1.14	1.01	0.40
		ID	0.67	1.13	1.40	1.03	1.25	1.13	-0.2	0.85	0.05	-6.4
	MI	IR	1.93	1.75	1.70	1.59	1.62	1.56	1.40	1.06	0.72	0.62
		ID	1.55	1.78	1.91	2.03	2.43	2.62	2.38	0.43	-3.3	-6.1
	SD	IR	2.72	1.66	2.13	2.06	2.10	2.24	1.80	1.65	1.67	-
		ID	0.43	0.33	0.59	0.72	0.92	1.31	1.08	0.90	1.20	1.44

IR - incidence ratio; ID - incidence difference (events/1000 pyrs)

6.4.3 Cox proportional hazard models of risk factors for Ischemic Heart Disease

The patterns observed for incidence of IHD within categories of each risk factor just described, suggest that the effect of the risk factors might be dependent both on age and the specific manifestation of IHD. This was examined in detail by testing the statistical significance of continuous values of SBP, DBP and BMI and the categorical representation of diabetes and smoking at the ages from 30 to 75 years using age specific Cox proportional hazard models. To examine the effects of each of the 5 risk factors, at each of the 10 ages, for the endpoints of IHD, AP, MI and SD, 200 Cox models were fit. The relative risks for disease, with 95% confidence intervals, were estimated from these models for each risk factor.

For each risk factor and endpoint combination, two further models were fit. First, the changing values of an individual's risk factor measured during follow-up were modeled using a time dependent covariate Cox proportional hazard model. Second, the effect of aging on each risk factor, that is, the varying effect of the risk factor with age, was tested by assessing the significance of the inclusion of an interaction term(s) in the model defined as the product of the risk factor and age. The likelihood ratio test was used to test the significance of the interaction effect. The estimate of the relative risk for a change in each risk factor, with and without interaction with age, for endpoints of IHD, AP, MI, and SD were calculated.

Every model included the year of examination to adjust both for temporal effects in the risk factor distributions over time as well as the changing incidence of IHD.

6.4.3.1 Models of Systolic Blood Pressure and Ischemic Heart Disease

The relative risk of IHD, AP, MI and SD associated with a 10 mm Hg difference in SBP at each five year examination age between 30 and 75 years is shown in Table 6.15. A 10 mm Hg difference in SBP at age 30 years was significantly associated with a 1.13 times increased risk of IHD (95% CI: 1.03,1.23). At this age SBP was not significantly associated with AP, but the 10 mm Hg difference in SBP in men 30 years of age increased the risk MI by 16% increased the risk of SD by 30%. For IHD, the magnitude of the relative risk was 1.17, 1.16 and 1.15 at ages 35, 40 and 45 years, respectively, and decreased to a smaller and non significant effect after age 65 years. The relative risk associated with SBP at every age was greatest for SD, and statistically significant at ages up to 70 years.

Table 6.15 Relative Risk, with 95% confidence intervals, for first manifestation of Ischemic Heart Disease, Angina Pectoris, Myocardial Infarction and Sudden Death associated with a 10 mm Hg difference in Systolic Blood Pressure.

Age	IHD	AP	MI	SD
30	1.13 1.03,1.23	1.04 0.90,1.19	1.16 1.02,1.32	1.30 1.03,1.66
35	1.17 1.10,1.25	1.18 1.06,1.30	1.15 1.05,1.26	1.25 1.04,1.50
40	1.16 1.10,1.22	1.14 1.05,1.24	1.15 1.06,1.24	1.26 1.10,1.45
45	1.15 1.10,1.20	1.14 1.07,1.22	1.12 1.05,1.20	1.29 1.17,1.43
50	1.12 1.08,1.17	1.11 1.04,1.18	1.10 1.04,1.17	1.26 1.14,1.38
55	1.16 1.12,1.21	1.17 1.10,1.24	1.14 1.07,1.21	1.24 1.12,1.37
60	1.11 1.06,1.15	1.10 1.03,1.17	1.06 0.99,1.13	1.27 1.16,1.39
65	1.11 1.05,1.17	1.11 1.02,1.20	1.09 1.01,1.18	1.19 1.04,1.36
70	1.08 0.99,1.62	1.01 0.89,1.16	1.08 0.97,1.20	1.22 1.01,1.49
75	1.12 0.98,1.27	0.99 0.78,1.27	1.20 1.02,1.42	1.01 0.67,1.52

Relative risks were estimated from age-specific Cox proportional hazard models. All models included SBP and year of examination.

The Cox time dependent covariate models incorporating the changing values of SBP with age are described in Table 6.16. The two columns under each endpoint heading

present the relative risk for a 10 year difference in age and a 10 mm Hg difference in SBP estimated from two models. The model described in the first column of the pair contained year of examination, age at examination and SBP; while the second model contained year of examination, age at examination, SBP and the product of age and SBP to represent the changing effect of SBP with age. A negative coefficient for the interaction term, in the second model implies that the relative risk for IHD associated with a difference in SBP decreases with advancing age. The statistical significance of the interaction term was tested by the likelihood ratio chi square test, and is presented at the center of the bottom of the two columns.

For all IHD types, the age adjusted relative risk for a 10 mm Hg difference in SBP was estimated to be 1.13 (95% CI: 1.10,1.17). A 10 year increase in age, adjusted for differences in SBP, held a 73% greater risk for IHD, (95% CI: 57%,90%). However, the interaction of SBP and age was statistically significant ($p<0.001$). The effect of a 10 year difference in age, on a 10 mm Hg difference in SBP, was estimated to be 0.94 (95% CI: 0.91,0.97). This implies that the effect of SBP depends upon age at examination, and that the relative risk associated with a 10 mm Hg difference in SBP declines by 6% with each 10 year advance in age.

The significant declining relative risk for AP with age and SBP ($p<0.001$) was similar to that found overall for IHD. The relative risk for AP associated with a 10 mm Hg difference in SBP was greatest in the younger men, decreased by 8% with each 10 years of age, i.e., the relative risk at the older age was only 0.92 (95% CI: 0.87,0.96)

times that of the relative risk at an age 10 years younger. This significantly decreasing relative risk with advancing age ceased to be associated with AP after age 65 years. The relative risk of MI did not significantly change with age with ($p>0.05$). A 10 mm Hg difference in SBP was associated with a 7% increased risk (95% CI: 2%,12%) of MI. Similarly, no trend of adjusted relative risk of SD with advancing age was apparent, as the interaction term for age and SBP was non-significant, ($p>0.10$). The age adjusted relative risk for SD of a 10 mm Hg difference in SBP, was estimated to be 1.24 (95% CI 1.14,1.34).

Table 6.16 Relative Risk, with 95% confidence intervals, for a 10 mm Hg difference in Systolic Blood Pressure estimated from time dependent Cox proportional hazard models.

Variable	Ischemic Heart Disease		Angina Pectoris		Myocardial Infarction		Sudden Death	
Age at examination (10 year difference)	1.73 1.57,1.90	3.95 2.55,6.10	1.78 1.54,2.06	6.16 3.22,11.8	1.69 1.47,1.95	3.02 1.55,5.90	1.70 1.30,2.23	2.20 0.69,6.98
SBP (10 mm Hg difference)	1.13 1.10,1.17	1.62 1.34,1.94	1.16 1.11,1.22	1.20 1.51,2.58	1.07 1.02,1.12	1.38 1.04,1.84	1.24 1.14,1.34	1.38 0.86,2.21
Age*SBP	-	0.94 0.91,0.97	-	0.92 0.87,0.96	-	0.96 0.91,1.01	-	0.98 0.91,1.06
-2 ln L (df)	206.7 (3)	221.2 (4)	111.2 (3)	125.6 (4)	62.7 (3)	65.8 (4)	45.4 (3)	45.6 (4)
Test for interaction χ^2 (df) p-value	14.5 (1) <0.001		14.4 (1) <0.001		3.1 (1) >0.05		0.2 (1) >0.10	

A main effects model with year, age and SBP and a second model including the age by SBP interaction term were fit for IHD, AP, MI and SD endpoints.

6.4.3.2 Models of Diastolic Blood Pressure and Ischemic Heart Disease

The relative risk of IHD associated with a 10 mm Hg difference in DBP was greatest in the younger men, as shown in Table 6.17. While the relative risk for a 10 mm Hg difference in DBP was greater than the corresponding relative risk for the same magnitude of difference in SBP (Table 6.15), the trend of relative risk of IHD for DBP with age was similar to that found for SBP. DBP remained significantly associated with IHD up to age 70 years and up to age 60 years for AP and SD. At each age, the relative risk for a difference in DBP was greater for SD, than for either AP or MI. At ages 45 through 60 years, the relative risk for AP was greater than that for MI, while from age 60 years to 70 years, the relative risk for MI was greatest.

Table 6.17 Relative Risk, with 95% confidence intervals, for Ischemic Heart Disease, Angina Pectoris, Myocardial Infarction and Sudden Death associated with a 10 mm Hg difference in Diastolic Blood Pressure estimated from age-specific Cox proportional hazard models.

Age	IHD	AP	MI	SD
30	1.24 1.10,1.40	1.13 0.94,1.36	1.21 1.02,1.44	1.83 1.31,2.57
35	1.30 1.19,1.41	1.34 1.17,1.53	1.28 1.13,1.44	1.23 0.95,1.60
40	1.24 1.16,1.33	1.21 1.08,1.36	1.23 1.11,1.37	1.35 1.12,1.65
45	1.28 1.19,1.36	1.31 1.19,1.45	1.23 1.12,1.36	1.30 1.08,1.58
50	1.25 1.18,1.34	1.29 1.17,1.42	1.20 1.09,1.32	1.34 1.12,1.60
55	1.24 1.16,1.33	1.26 1.14,1.40	1.20 1.08,1.34	1.29 1.07,1.56
60	1.16 1.07,1.26	1.16 1.02,1.31	1.09 0.97,1.24	1.41 1.14,1.74
65	1.21 1.09,1.34	1.13 0.96,1.33	1.26 1.09,1.46	1.29 0.98,1.70
70	1.17 1.00,1.36	1.00 0.78,1.30	1.28 1.04,1.57	1.21 0.80,1.83
75	1.17 0.90,1.51	0.85 0.53,1.36	1.38 0.99,1.92	1.19 0.55,2.58

Relative risks were estimated from age-specific Cox proportional hazard models. All models included DBP and year of examination.

A significantly decreasing relative risk of IHD with age was apparent as for DBP, as shown in Table 6.18. The age by DBP interaction was negative and statistically significant ($p<0.01$), with the effect of a 10 mm Hg difference in DBP on risk of IHD estimated to decrease by 8% (relative risk = 0.92, 95% CI: 0.87,0.97) with each 10 years of age. The relative risk of AP associated with a 10 mm Hg difference in DBP decreased with advancing age by 9% (relative risk = 0.91, 95% CI: 0.84,0.98) with each 10 years of age. An 11% decrease in relative risk of MI associated with a 10 mm Hg difference in DBP (relative risk = 0.89, 95% CI: 0.82,0.97) was found for each 10 years of age, in contrast to a non-significant decreasing relative risk with age for SBP and MI. No significant trend with age for a changing effect of the relative risk for SD with DBP was apparent ($p>0.10$). The relative risk of SD of a 10 mm Hg difference in DBP, over all ages, was estimated to be 1.29 (95% CI 1.10,1.52).

Table 6.18 Relative Risk, with 95% confidence intervals, for a 10 mm Hg difference in Diastolic Blood Pressure estimated from time dependent Cox proportional hazard models.

Variable	Ischemic Heart Disease		Angina Pectoris		Myocardial Infarction		Sudden Death	
Age at examination (10 year difference)	1.84 1.68,2.02	3.72 2.36,5.86	1.93 1.67,2.22	4.36 2.20,8.63	1.75 1.52,2.01	4.40 2.30,8.45	1.94 1.49,2.52	1.03 0.25,4.21
DBP (10 mm Hg difference)	1.24 1.17,1.31	2.03 1.48,2.79	1.30 1.20,1.42	2.30 1.43,3.70	1.17 1.08,1.28	2.25 1.42,3.57	1.29 1.10,1.52	0.83 0.31,2.22
Age*DBP	-	0.92 0.87,0.97	-	0.91 0.84,0.98	-	0.89 0.82,0.97	-	1.08 0.91,1.23
-2 ln L (df)	201.1 (3)	210.2 (4)	107.5 (3)	112.8 (4)	67.6 (3)	75.1 (4)	30.6 (3)	31.4 (4)
Test for interaction χ^2 (df) p-value	9.1 (1) <0.01		5.3 (1) <0.05		7.5 (1) <0.01		0.8 (1) >0.10	

A main effects model with year of examination, age and DBP and a second model including the age by DBP interaction term were fit for IHD, AP, MI and SD endpoints.

6.4.3.3 Models of Body Mass Index and Ischemic Heart Disease

BMI was a significant risk factor for IHD from age 30 years through to age 65 years as shown in Table 6.19. The importance of BMI across these ages was also consistently seen for AP. For all manifestations of IHD, the greatest effects of a 5 Kg/m^2 difference in BMI were found at age 40 and 45 years. At these ages, the greatest effect was on subsequent risk of SD with effects of similar magnitude for AP and MI. BMI was not significantly associated with MI after age 45 years, and not with SD after age 50 years.

There was no evidence of any age effect on the magnitude of the relative risk for IHD associated with BMI ($p>0.90$), as shown in Table 6.20. Overall, the effect of a difference in 5 kg/m^2 in BMI carried with it a 26% increased risk of IHD (95% CI: 14%,40%). There was no evidence of any age effect on the magnitude of the relative risk associated with BMI ($p>0.10$) and AP, where a difference in 5 kg/m^2 in BMI carried with it a 30% increased risk of AP over all ages (95% CI: 9%,54%). The effect of BMI on risk of MI was significant at younger ages, 40 and 45 years. A 5 kg/m^2 difference in BMI at age 40 carried with it a 34% increased risk of MI, and a 25% increased risk at age 45 years. There was no evidence of any age effect on the magnitude of the relative risk associated with BMI ($p>0.90$). Overall a relative risk of 1.22 (95% CI: 1.04,1.43) was estimated. The effect of BMI on risk of SD was significant at young ages, from 35 years up to 50 years. The relatively constant effect a 5 kg/m^2 difference in BMI carried with it an increased risk of SD estimated to be 1.28 (95% CI 0.93,1.76) with no evidence of any age effect on the magnitude of the effect of BMI ($p>0.10$).

Table 6.19 Relative Risk, with 95% confidence intervals, for Ischemic Heart Disease, Angina Pectoris, Myocardial Infarction and Sudden Death associated with a 5 kg/m^2 difference in Body Mass Index estimated from age-specific Cox proportional hazard models.

Age	IHD	AP	MI	SD
30	1.22 1.02,1.46	1.42 1.07,1.88	1.02 0.78,1.33	1.47 0.87,2.49
35	1.24 1.08,1.42	1.26 1.01,1.56	1.14 0.93,1.38	1.72 1.16,2.55
40	1.39 1.23,1.57	1.34 1.11,1.63	1.34 1.12,1.60	1.74 1.25,2.44
45	1.32 1.17,1.49	1.26 1.05,1.51	1.25 1.05,1.49	1.90 1.38,2.61
50	1.25 1.10,1.41	1.24 1.03,1.50	1.18 0.98,1.42	1.56 1.12,2.17
55	1.24 1.09,1.42	1.39 1.14,1.69	1.12 0.91,1.37	1.22 0.84,1.77
60	1.22 1.05,1.42	1.34 1.07,1.68	1.11 0.89,1.40	1.22 0.79,1.88
65	1.24 1.03,1.51	1.30 0.97,1.74	1.15 0.87,1.52	1.47 0.86,2.53
70	1.26 0.94,1.70	1.20 0.71,2.02	1.46 1.00,2.13	0.58 0.20,1.69
75	1.14 0.70,1.87	1.07 0.43,2.64	1.34 0.71,2.50	0.56 0.10,2.93

Relative risks were estimated from age-specific Cox proportional hazard models. All models included BMI and year of examination.

Table 6.20 Relative Risk, with 95% confidence intervals, for a 5 kg/m^2 difference in Body Mass Index estimated from time dependent Cox proportional hazard models.

Variable	Ischemic Heart Disease		Angina Pectoris		Myocardial Infarction		Sudden Death	
Age at examination (10 year difference)	1.98 1.79,2.20	2.73 1.59,4.68	1.98 1.68,2.32	2.78 1.19,6.50	2.00 1.73,2.32	2.50 1.14,5.47	1.92 1.43,2.59	3.68 0.78,17.3
BMI (5 kg/m^2 difference)	1.26 1.13,1.40	1.83 0.97,3.44	1.30 1.09,1.54	1.94 0.72,5.23	1.22 1.04,1.43	1.58 0.63,3.96	1.28 0.93,1.76	2.72 0.45,16.5
Age*BMI	-	0.94 0.84,1.04	-	0.93 0.79,1.10	-	0.96 0.82,1.12	-	0.88 0.64,1.19
-2 ln L	158.9 (3)	160.3 (4)	64.7 (3)	65.3 (4)	78.5 (3)	78.8 (4)	17.2 (3)	17.9 (4)
Test for interaction χ^2 (df) p-value	1.4 (1) >0.10		0.6 (1) >0.10		0.3 (1) >0.10		0.7 (1) >0.10	

A main effects model with year, age and BMI and a second model including the age by BMI interaction term were fit for IHD, AP, MI and SD endpoints.

6.4.3.4 Models of Diabetes Mellitus and Ischemic Heart Disease

The prevalence of DM was less than 1 percent before age 50, and therefore the relationship of diabetes to IHD was not examined before this age in the Cox models shown in Table 6.21. Diabetics at ages 50 through 65 years were at a risk for IHD at least double that of non-diabetics. A gradient of the effect of diabetes with age was not statistically significant, ($p>0.10$) and the relative risk of IHD for DM was estimated to be 1.93 (95% CI 1.49,2.52), as shown in Table 6.22.

The risk of AP for diabetics was significant only at age 50 years. Further, investigation revealed that of the few diabetics known at age 50 years, six were diagnosed

with AP before their 55th birthday. Diabetics up to age 65 years remained at a significantly increased risk of MI and SD, where overall relative risks of 1.99 (95% CI 1.36,2.92) and 2.12 (95% CI 1.02,4.38), respectively, were estimated for diabetic compared to non-diabetic men. A gradient of the effect of diabetes with age was not statistically significant for any IHD endpoint.

Table 6.21 Relative Risk, with 95% confidence intervals, for Ischemic Heart Disease, Angina Pectoris, Myocardial Infarction and Sudden Death associated with presence of Diabetes Mellitus estimated from age-specific Cox proportional hazard models.

Age	IHD	AP	MI	SD
50	2.72 1.68,4.41	3.08 1.52,6.22	2.41 1.14,5.10	2.69 0.66,11.0
55	2.12 1.44,3.12	1.59 0.82,3.10	2.19 1.23,3.90	3.77 1.64,8.64
60	1.99 1.38,2.86	1.63 0.89,2.99	2.17 1.28,3.66	2.58 1.04,6.44
65	2.54 1.76,3.66	1.45 0.71,2.96	3.16 1.92,5.18	4.33 1.80,10.4
70	1.14 0.58,2.23	0.69 0.17,2.82	1.22 0.49,3.03	2.17 0.50,9.47
75	1.00 0.31,3.24	-	0.59 0.08,4.38	9.66 1.65,56.5

The prevalence of diabetes mellitus was <1% at this age and not considered in this model
Relative risks were estimated from age-specific Cox proportional hazard models. All models included an indicator for DM and year of examination.

Table 6.22 Relative Risk, with 95% confidence intervals, for presence of Diabetes Mellitus estimated from time dependent Cox proportional hazard models.

Variable	Ischemic Heart Disease		Angina Pectoris		Myocardial Infarction		Sudden Death	
Age at examination (10 year difference)	1.71 1.53,1.90	1.72 1.54,1.92	1.66 1.40,1.97	1.71 1.44,2.03	1.72 1.46,2.02	1.71 1.44,2.02	1.84 1.36,2.48	1.78 1.31,2.44
DM (present / not present)	1.93 1.49,2.52	3.60 0.44,29.2	1.82 1.20,2.76	44.7 1.4,1472	1.99 1.36,2.92	1.19 0.06,23.5	2.12 1.02,4.38	0.28 0.01,68.8
Age*DM	-	0.91 0.66,1.25	-	0.60 0.34,1.06	-	1.08 0.69,1.70	-	1.56 0.61,3.07
-2 ln L	104.6 (3)	105.0 (4)	39.1 (3)	42.4 (4)	49.3 (3)	49.4 (4)	17.4 (3)	17.9 (4)
Test for interaction χ^2 (df) p-value	0.4 (1) >0.10		3.3 (1) >0.05		0.1 (1) >0.10		0.5 (1) >0.10	

A main effects model with year, age and DM and a second model including the age by DM interaction term were fit for IHD, AP, MI and SD endpoints occurring after age 50 years.

6.4.3.5 Models of Smoking and Ischemic Heart Disease

Smokers at age 30 through 55 years were at an increased risk of IHD. Smokers incurred a risk of IHD that was 1.68 (95% CI 1.24,2.28) times greater than that of non-smokers at age 30 years, as shown in Table 6.23. This relative risk diminished with age to 1.42 (95% CI 1.13,1.79) at age 55 years and was non-significant at ages after that. The interaction terms describing a changing effect of smoking with age were significant and negative ($p<0.001$), indicating a decreasing risk of IHD for smokers relative to non-smokers with advancing age, as shown in Table 6.24.

Table 6.23 Relative Risk, with 95% confidence intervals, for Ischemic Heart Disease, Angina Pectoris, Myocardial Infarction and Sudden Death associated with Current Smoking relative to Never Smoked, estimated from age-specific Cox proportional hazard models.

Age	IHD	AP	MI	SD
30	1.68 1.24,2.28	1.34 0.87,2.05	1.95 1.22,3.11	2.77 0.85,9.05
35	1.66 1.32,2.09	1.52 1.08,2.14	1.79 1.27,2.52	1.72 0.82,3.62
40	1.69 1.35,2.10	1.55 1.11,2.16	1.73 1.25,2.39	2.18 1.05,4.55
45	1.48 1.20,1.82	1.27 0.93,1.72	1.61 1.17,2.21	1.99 0.99,4.00
50	1.48 1.19,1.84	1.25 0.91,1.73	1.60 1.15,2.23	2.06 1.02,4.15
55	1.42 1.13,1.79	1.16 0.83,1.63	1.54 1.09,2.19	2.20 1.08,4.49
60	1.27 0.98,1.66	1.03 0.68,1.54	1.40 0.95,2.06	1.77 0.81,3.87
65	1.08 0.77,1.51	1.04 0.61,1.77	1.02 0.63,1.65	1.56 0.56,4.34
70	0.88 0.54,1.44	0.81 0.33,2.00	0.82 0.43,1.57	1.46 0.37,5.87
75	0.58 0.25,1.36	0.16 0.02,1.37	0.75 0.27,2.08	-

Relative risks were estimated from age-specific Cox proportional hazard models. All models included indicators for smoking status and year of examination.

Smokers at younger ages, age 35 and 40 years, were at a risk of AP about one and a half times greater than men who had never smoked. The interaction terms for age and smoking were non-significant ($p>0.10$), supporting evidence for a constant but non-significant effect of smoking on risk of AP with advancing age. Overall, a risk ratio of 1.23 (95% CI 0.90,1.68) was estimated for smoking and AP, but non significant, suggesting that smoking over all ages, specifically from age 50 years or older, was not significantly associated with an increased risk of AP. Men who smoked up to age 55 years were at an increased risk of MI. Smokers incurred a risk of MI that was almost two fold greater than risk for non-smokers at age 30 years. This relative risk diminished with age and was non-significant after age 55 years. The interaction term for age and smoking on risk of MI was significant and negative ($p<0.001$), indicating a significantly decreasing risk of MI for smokers relative to non-smokers with advancing age. Between ages 40 and 55 years, smokers were at an increased risk of SD about 2 times greater than non-smokers, and greater than the risk associated with any other manifestation of IHD. This relative risk diminished with age and was non-significant after age 55 years. The interaction terms for age and smoking were significant and negative ($p<0.001$), indicating a significantly decreasing risk of SD for smokers relative to non-smokers with advancing age.

Table 6.24 Relative Risk, with 95% confidence intervals, for Smoking estimated from time dependent Cox proportional hazard models.

Variable	Ischemic Heart Disease		Angina Pectoris		Myocardial Infarction		Sudden Death	
Age at examination (10 year difference)	1.84 1.68,2.02	2.42 2.02,2.91	1.94 1.68,2.23	2.25 1.73,2.93	1.75 1.52,2.01	2.64 2.00,3.47	1.89 1.45,2.45	2.53 1.33,4.82
Current Smoker (relative to never smoked)	1.65 1.34,2.04	11.9 3.47,40.7	1.34 0.98,1.83	4.66 0.80,27.1	1.85 1.36,2.53	42.5 6.45,280.	2.41 1.18,4.93	4.70 0.06,384.
Age* Current Smoker	-	0.72 0.59,0.88	-	0.81 0.60,1.08	-	0.60 0.44,0.80	-	0.91 0.46,1.82
-2 ln L	266.6 (5)	302.8 (8)	95.6 (5)	96.1 (8)	108.6 (5)	140.8 (8)	93.7 (5)	112.2 (8)
Test for interaction χ^2 (df) p value	36.2 (3) <0.001		0.5 (3) >0.10		32.2 (3) <0.001		18.5 (3) <0.001	

A main effects model with year, age and smoking category indicators and a second model including the age by smoking interaction terms were fit for IHD, AP, MI and SD endpoints.

6.4.3.6 Testing the proportionality assumption for risk factors in Cox proportional hazard models

Each risk factor is assumed to have a constant, proportional effect, on the hazard function in the Cox model, independent of time under observation. This assumption was examined for models of IHD, AP, MI and SD by testing the significance of an interaction term for the risk factor and time under observation. If the proportionality assumption holds, the relative risk of IHD associated with the difference in two values of a risk

factor, determined at one point in time, will remain constant over the time period modeled.

With IHD, the proportional hazards assumption for SBP and DBP held at all ages after 40 years, except age 60 years for SBP and 75 years for DBP (p-values at these ages between 0.01 and 0.05). The interaction with BMI and time was non-significant (all $p>0.05$) for BMI at exams after age 35 as well as for all models of DM (except at age 60 years). The proportionality assumption for smoking was significant ($p<0.05$) at younger ages, up to age 50 years, suggesting a changing effect of smoking status at younger ages on risk of IHD. Thus, the relative risk of IHD estimated at most older ages for the risk factors determined at these ages can be assumed to be constant over the entire follow-up interval.

The tests for the proportionality assumption of the hazard function for AP were non-significant (all $p>0.05$) for BMI at all ages except at age 35 years. The proportional hazards assumption for SBP and DBP held after age 45 years for SBP and DBP. The proportionality assumption held for smoking effects at all ages. Thus, the relative risk of AP estimated at most older ages for the risk factors examined can be assumed to be constant over the entire follow-up interval.

The tests for the proportionality assumption of risk factors and MI were significant ($p<0.05$) prior to age 45 for SBP and prior to age 40 for DBP. The test for the proportional hazards assumption for smoking and MI was significant ($p<0.05$) for

smoking at younger ages, up to age 50 years, suggesting that the effects of these factors at younger ages might be changing with longer follow-up.

The tests for the proportionality assumption of the hazard function for SD were non-significant (all $p>0.05$) for BMI and DM. The proportional hazards assumption for SBP and DBP held at all ages, except age 50 years for DBP. Thus, the relative risk of SD estimated at most ages for the risk factors examined can be assumed to be constant over the entire follow-up interval.

6.4.3.7 Summary of modeling aging effects on risk factors for Ischemic Heart Disease

A summary of the results of the age-specific models of the five risk factors for IHD and its three specific manifestations appear in Table 6.25. Blood pressure, both SBP and DBP, are significant risk factors for IHD and each of its manifestations. The effect on IHD and AP of any constant difference, either in SBP or DBP, with advancing age was significantly declining. The effect SBP and DBP have on risk of SD did not significantly change with age. Both remained important risk factors for SD through to age 65 years. There was a declining effect with age for DBP and MI, but a constant effect with age for SBP and MI. The effect of BMI on risk of IHD did not significantly change with age. The effect of BMI was most apparent for AP, where a 5 kg/m^2 difference in BMI incurred a 1.30 increased risk. BMI was not statistically significant over all ages for SD. Smoking had a declining effect with age for IHD. The effect of

smoking was not significant for AP, and smoking had a significantly declining effect with age for MI and SD.

Table 6.25 Summary of the significance and direction of the trend with age for the effect of each risk factor based the Cox proportional hazard modeling of IHD and its manifestations

Risk Factor	Ischemic Heart Disease	Angina Pectoris	Myocardial Infarction	Sudden Death
Systolic Blood Pressure	decreasing	decreasing	constant	constant
Diastolic Blood Pressure	decreasing	decreasing	decreasing	constant
Body Mass Index	constant	constant	constant	not significant
Diabetes Mellitus	constant	constant	constant	constant
Smoking	decreasing	not significant	decreasing	decreasing

decreasing ..... a significant negative trend with age ($p<0.05$) was found for the effect of this risk factor
constant ..... a constant effect, with no significant trend with age ($p>0.05$), was found for this risk factor
not significant ..... this risk factor was not significant ($p>0.05$)

6.4.4 Multivariate Cox proportional hazard modeling of risk factors for Ischemic Heart Disease

In order to assess the joint independent effect of the risk factors at each age from 30 to 75 years, the best fitting forward stepwise multivariate Cox proportional hazard models for IHD, AP, MI and SD were determined. Estimates of the relative risk with 95% confidence intervals were calculated for significant parameters. Year of examination was included in all models.

6.4.4.1 Age specific multivariate models for Ischemic Heart Disease

As shown in Table 6.26, DBP was significant in forward stepwise models of IHD up to age 50 years, where after SBP was statistically significant to age 70 years. Thus, blood pressure was important in all multivariate models up to age 70 years. At younger ages, 40, 45 and 55 years, BMI was significant in the stepwise models of IHD. At ages 50 through 65 years DM contributed significantly to these models. Smoking was statistically significant in models up to age 55 years, with current smokers at a significantly increased risk of IHD relative to those who never smoked, and former smokers at no increased risk of IHD relative to those who never smoked.

Table 6.26 Multivariate Relative Risk, with 95% confidence intervals, for Ischemic Heart Disease estimated from the best fit stepwise Cox proportional hazard model.

Age (years)	SBP (10 mm Hg difference)	DBP (10 mm Hg difference)	BMI (5 kg/m^2 difference)	DM (diabetic vs non-diabetic)	Current Smoker (vs never smoked)	Former Smoker (vs never smoked)
30	-	1.23 1.09,1.39	-	*	1.70 1.25,2.31	1.22 0.71,2.10
35	-	1.31 1.20,1.43	-	*	1.71 1.36,2.16	1.12 0.78,1.63
40	-	1.20 1.11,1.30	1.28 1.13,1.46	*	1.65 1.32,2.06	1.28 0.96,1.71
45	-	1.23 1.15,1.32	1.19 1.05,1.34	*	1.45 1.17,1.79	1.12 0.87,1.44
50	-	1.25 1.17,1.34	-	2.75 1.67,4.53	1.43 1.14,1.79	1.17 0.91,1.50
55	1.13 1.08,1.18	-	1.15 1.01,1.32	2.24 1.51,3.33	1.40 1.10,1.78	1.11 0.86,1.42
60	1.09 1.04,1.14	-	-	1.81 1.19,2.76	-	-
65	1.11 1.05,1.18	-	-	2.52 1.67,3.79	-	-
70	1.10 1.00,1.20	-	-	-	-	-
75	-	-	-	-	-	-

- this variable did not enter the stepwise model at p=0.05

* Prevalence of Diabetes Mellitus was <1% at this age and not considered in this model

6.4.4.2 Age specific multivariate models for Angina Pectoris

In stepwise models for AP, DBP was found to be more important in contrast to SBP at younger ages, up to age 50 years, with SBP significant in models at age 55 and 65 years, as shown in Table 6.27. After age 65 years of age, neither SBP nor DBP added significantly to the modeling of AP. BMI contributed significantly to the stepwise models of AP at younger ages, age 30 and 40 years as well as at later ages, 55 and 60 years. DM was only significant at age 50 years of age. The significance of DM for AP at this age was highly influenced by 6 diabetics who had an AP diagnosis in their early 50s. Smoking was statistically significant in models of AP only at age 35 and 40 years, after which time the risk of AP for smokers relative to non-smokers was not statistically significant. No variables were significant in models at age 70 or 75 years.

Table 6.27 Multivariate Relative Risk, with 95% confidence intervals, for Angina Pectoris estimated from the best fit stepwise Cox proportional hazard model

Age (years)	SBP (10 mm Hg difference)	DBP (10 mm Hg difference)	BMI (5 kg/m^2 difference)	DM (diabetic vs non-diabetic)	Current Smoker (vs never smoked)	Former Smoker (vs never smoked)
30	-	-	1.42 1.07,1.88	*	-	-
35	-	1.37 1.20,1.58	-	*	1.57 1.10,2.22	1.05 0.60,1.85
40	-	1.19 1.05,1.34	1.26 1.03,1.53	*	1.49 1.07,2.08	1.30 0.84,2.00
45	-	1.29 1.17,1.44	-	*	-	-
50	-	1.31 1.18,1.45	-	2.68 1.27,5.69	-	-
55	1.13 1.06,1.21	-	1.28 1.04,1.56	-	-	-
60	-	-	1.34 1.07,1.68	-	-	-
65	1.11 1.02,1.20	-	-	-	-	-
70	-	-	-	-	-	-
75	-	-	-	-	-	-

* Prevalence of Diabetes Mellitus was <1% at this age and not considered in this model
- variable did not enter stepwise model at p=0.05

6.4.4.3 Age specific multivariate for Myocardial Infarction

As shown in Table 6.28, generally DBP was found to be more important than SBP in models for MI. BMI was significant only at age 40 years. The significance at ages 50 through 65 years of DM was most important for MI, with diabetics being at more than twice the risk of MI compared to non-diabetics. Smoking was statistically significant in models of MI up to age 50 years of age, with smokers being at at least a 50% greater risk of MI relative to non-smokers.

Table 6.28 Multivariate Relative Risk, with 95% confidence intervals, for Myocardial Infarction estimated from the best fit stepwise Cox proportional hazard model.

Age (years)	SBP (10 mm Hg difference)	DBP (10 mm Hg difference)	BMI (5 kg/m^2 difference)	DM (diabetic vs non-diabetic)	Current Smoker (vs never smoked)	Former Smoker (vs never smoked)
30	1.15 1.01,1.31	-	-	*	1.97 1.24,3.14	1.32 0.58,2.99
35	-	1.28 1.12,1.45	-	*	1.85 1.31,2.61	1.34 0.79,2.25
40	-	1.19 1.06,1.33	1.25 1.04,1.50	*	1.70 1.23,2.36	1.29 0.84,1.97
45	-	1.24 1.12,1.37	-	*	1.53 1.11,2.10	1.23 0.85,1.80
50	-	1.18 1.07,1.31	-	2.60 1.22,5.51	1.50 1.07,2.10	1.24 0.85,1.79
55	1.13 1.06,1.21	-	-	2.30 1.25,4.21	-	-
60	-	-	-	2.17 1.28,3.66	-	-
65	-	1.26 1.05,1.50	-	3.40 1.97,5.86	-	-
70	-	1.34 1.06,1.69	-	-	-	-
75	1.20 1.02,1.42	-	-	-	-	-

\- variable did not enter stepwise model at p=0.05

* The prevalence of Diabetes Mellitus was <1% and not considered in this model

6.4.4.4 Age specific multivariate models for Sudden Death

SBP rather than DBP was more strongly associated with SD at ages from 40 through 65 years, as shown in Table 6.29. BMI was significant in the stepwise models of SD up to age 45 years. Diabetics at ages 55 and 65 years were at significantly increased risk of SD. Current smokers at ages 40 and 55 years were at a greater risk of SD relative to non-smokers, while former smokers were at no significantly increased risk of SD over those who never smoked. None of the risk factors were significantly associated with SD at age 70 or 75 years.

Table 6.29 Multivariate Relative Risk, with 95% confidence intervals, for Sudden Death estimated from the best fit stepwise Cox proportional hazard model.

Age (years)	SBP (10 mm Hg difference)	DBP (10 mm Hg difference)	BMI (5 kg/m^2 difference)	DM (diabetic vs non-diabetic)	Current Smoker (vs never smoked)	Former Smoker (vs never smoked)
30	-	1.83 1.31,2.57	-	*	-	-
35	-	-	1.72 1.16,2.55	*	-	-
40	1.22 1.05,1.41	-	1.54 0.09,2.16	*	2.12 1.02,4.42	1.14 0.41,3.15
45	1.23 1.10,1.37	-	1.63 1.17,2.26	*	-	-
50	1.26 1.14,1.38	-	-	-	-	-
55	1.18 1.06,1.32	-	-	3.91 1.69,9.05	2.32 1.10,4.92	0.92 0.40,2.13
60	1.27 1.16,1.39	-	-	-	-	-
65	1.27 1.08,1.49	-	-	3.17 1.09,9.24	-	-
70	-	-	-	-	-	-
75	-	-	-	-	-	-

\- variable did not enter stepwise model at $p<0.05$

* The prevalence of Diabetes Mellitus was <1% and not considered in this model

6.4.4.5 Summary of multivariate modeling of risk factors for Ischemic Heart Disease

The relative independent importance of these risk factors for IHD and each manifestation of IHD at the age from 30 to 75 years are summarized in Table 6.30. BP was an important risk factor in models of IHD up to age 70 years. DBP was the BP to enter stepwise models up to age 50 and SBP became a more powerful BP variable in models for IHD from age 55 through to age 70 years. However, a diminishing effect of either BP measurement was found with advancing age. While DBP was more important than SBP in models for AP and MI at younger ages, SBP was the more important of the two at ages 40 through 65 years for SD.

BMI at younger ages, 35 and 40 years, was found to be significantly associated with IHD. At age 40 years, BMI significantly contributed to all four models of IHD endpoints. BMI at ages 35, 40 and 45 years also was significant in models of SD. Again at age 55 and 60 years, higher BMI incurred a greater risk of IHD, specifically for AP.

DM in the four age specific models from age 50 through 65 years had a consistent and significant independent association with MI. Only at age 50 years did DM contribute to a model for AP and at ages 55 and 65 years for SD.

Smoking at age 30 years was significant in models for IHD, MI and SD, and from age 35 years for AP. By age 60, the effect of smoking had diminished to be no longer independently statistically significant in models for IHD or any of the manifestations. The independent contribution of smoking was only significant in models for AP up to age

40, while it remained significant to age 50 for MI. Smoking was significant in models for SD at ages 40 and 55 years.

Table 6.30 Summary of the significant risk factors in age-specific forward stepwise Cox proportional hazard models of Ischemic Heart Disease, Angina Pectoris, Myocardial Infarction and Sudden Death.

Age	Models for IHD	Models for AP	Models for MI	Models for SD
30	_ D _ - T	_ _ B - _	S _ _ - T	_ D _ - _
35	_ D B - T	_ D _ - T	_ D _ - T	_ _ B - _
40	_ D B - T	_ D B - T	_ D B - T	S _ B - T
45	_ D _ - T	_ D _ - _	_ D _ - T	S _ B - _
50	_ D _ _ T	_ D _ M _	_ D _ M T	S _ _ _ _
55	S _ B M T	S _ B _ _	S _ _ M _	S _ _M T
60	S _ _ M _	_ _ B _ _	_ _ _ M _	S _ _ _ _
65	S _ _ M _	*	_ D _ M _	S _ _ M _
70	S _ _ _ _	*	_ D _ _ _	*
75	*	*	S _ _ _ _	*

\- diabetes mellitus was not considered in models before age 50 years
* no variable entered the stepwise model at $p<0.05$
S - systolic blood pressure;
D - diastolic blood pressure;
B - body mass index;
M - diabetes mellitus;
T - smoking (tobacco)

6.5 Tracking risk factors in individuals and incidence Ischemic Heart Disease

6.5.1 Level, trend and variability of continuous risk factors

It has been earlier described that IHD was detected in cohort members at ages as young as 30-34 years, and that incidence of IHD increased with age in this cohort at least until age 80-84 years. Also, it has been shown that some of the traditional risk factors for IHD, specifically SBP, DBP and smoking have effects that tend to decrease in magnitude and statistical significance with age. The effect of BMI on incidence of IHD was most pronounced at younger ages. Evidence for tracking of SBP, DBP and BMI has been established, both in the lower end and upper end of their distributions, and specifically from younger ages, before age 50 years. It is therefore of interest to determine whether aspects of tracking of continuous risk factors from younger ages would significantly contribute to models of IHD developing in later life.

Patterns of SBP, DBP and BMI in individuals that describing the relationship of repeated measurements over time with age up to 50, 60 and 70 years were considered as indicators of tracking possible additional risk factors for development of IHD after these ages. The age specific percentile of every measurement of SBP, DBP and BMI for each subject was calculated as described in Section 5.9.2.1. For each of these three risk factors, three statistics were calculated, at 50, 60 and 70 years of age. The mean of the percentiles of all measurements from entry to these ages was called level. The slope of the ordinary least squares regression line of the percentile on age was called trend. The

root mean square error of the deviations about the least squares regression line was called variability.

The 5th and 95th percentiles, the tertiles and the median of the distributions of level, trend and variability for SBP, DBP, and BMI measurements prior to 50, 60 and 70 years of age are shown in Table 6.31. If "perfect tracking" were present for a variable, the distribution of "level" would be uniform. That is, at the 5th percentile 5% of subjects would have an average level of 5.0, the lower tertile at P33 would be 33.3, the median (P50) would be 50.0 and so on. The trend and variability would be zero.

"Level" for a subject is an indication of the average position maintained relative to others in the distribution based on his prior measurements. For example, at age 50 years, the average percentile level of prior SBP measurements for one third of the subjects (P33) was 43.0 or less. That is, one third of the subjects at age 50 years had, on the average, age-specific SBP percentile levels of their prior measurements at the 43rd percentile or lower. The average percentile of the lowest 5 percent of the subjects at age 50 years was 21.3 or less and 5 percent of subjects had an average level of 85.8 or higher. The average percentile of all previous BMI measurements was more than 64.9 for the top one third of men at age 50 years. For an individual, a "trend" with a negative sign, suggests a pattern of decreasing percentile rank with age, while a positive sign for "trend" suggests that an individual's rank in the distribution relative to others was increasing with age. A "zero trend" identifies subjects whose percentile rank remained unchanged with age. Consequently, a zero trend if accompanied with low variability indicates strong

evidence for tracking. High "variability" in the trend, measured by the root mean square error, is indicative of lability of BP or fluctuating, increases and decreases in BMI. These three statistics, derived from individual regression equations based on the measurements to age 50, 60 and 70 years for each subject were calculated for SBP, DBP and BMI.

The distribution of level, trend and variability were similar for SBP and DBP measurements. A higher degree of tracking for BMI is reflected in the distribution of level at each age, where the value of "level" for each percentile are close in value to the percentile itself. This is consistent with the higher correlation and higher relative likelihood measures for BMI compared to those for SBP or DBP.

Table 6.31 Percentiles of level, trend and variability distributions for SBP, DBP and BMI, at age 50, 60 and 70 years.

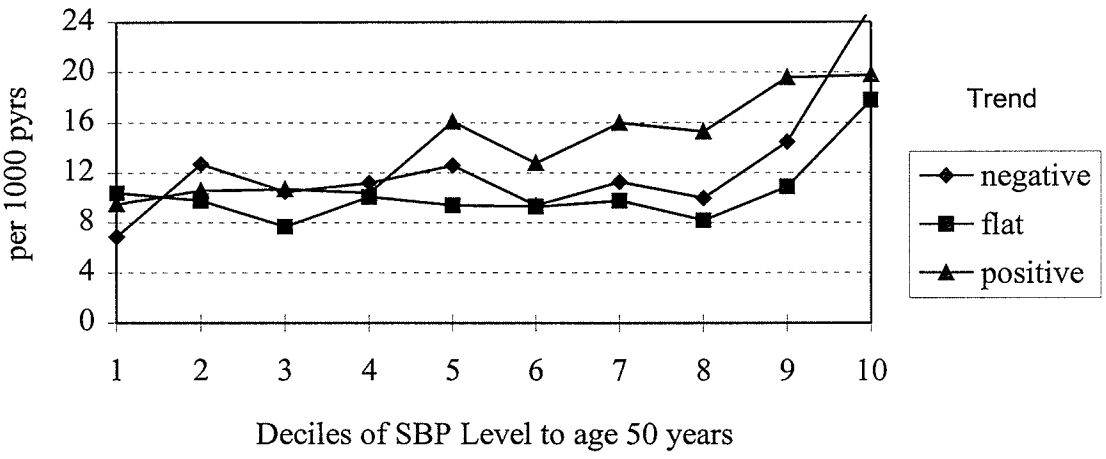
	Tracking Variable	Age	P5	P33	P50	P67	P95
SBP	Level	50	21.3	43.0	51.8	61.1	85.8
		60	21.2	41.8	50.4	59.0	83.0
		70	21.8	41.3	50.2	58.5	79.3
	Trend	50	-3.0	-0.7	-0.1	0.7	3.3
		60	-1.8	-0.5	-0.1	0.4	2.0
		70	-1.3	-0.3	0.0	0.4	1.7
	Variability	50	6.4	16.8	20.1	23.4	33.3
		60	9.5	17.8	20.5	22.9	30.3
		70	11.9	18.6	20.8	22.9	28.6
DBP	Level	50	24.5	45.9	54.6	63.1	85.2
		60	25.2	45.1	53.0	61.1	82.4
		70	26.4	44.9	52.8	60.1	79.2
	Trend	50	-3.1	-0.7	0.0	0.7	3.0
		60	-1.9	-0.5	-0.1	0.4	1.9
		70	-1.4	-0.3	0.0	0.4	1.5
	Variability	50	6.7	17.8	21.6	24.7	33.8
		60	10.7	19.1	21.8	24.2	30.9
		70	12.7	19.8	22.0	24.2	29.9
BMI	Level	50	7.2	35.2	50.0	64.9	92.2
		60	7.5	35.4	49.0	63.7	90.9
		70	8.3	35.1	47.4	63.2	90.5
	Trend	50	-2.0	-0.4	0.0	0.6	2.5
		60	-1.5	-0.3	0.0	0.4	1.7
		70	-1.2	-0.2	0.0	0.4	1.4
	Variability	50	1.6	6.2	8.3	10.5	18.6
		60	2.5	7.4	9.4	11.5	18.6
		70	3.0	7.9	9.8	11.9	18.7

Level	percentile of all measurements up to this age
Trend	least squares regression coefficient for percentile on age
Variability	root mean square error of the regression line of percentile on age

6.5.2 The relationship of Systolic Blood Pressure tracking to incidence of Ischemic Heart Disease

To examine the association between indicators of SBP tracking and IHD, incidence of IHD per 1,000 pyrs after age 50 years was plotted as shown in Figure 6.16. Overall, the incidence of IHD after age 50 years was 12.0 per 1,000 pyrs. Within deciles of "SBP level", incidence was plotted for subjects with low, flat and positive trends defined as trends in the lowest, middle and highest tertile of the distribution of slopes. Those with flat trends, i.e. those whose SBP tended to track relative to others before age 50 years, had a lower incidence of IHD compared to either of the other two groups where SBP percentile increased (positive trend) or decreased (negative trend). This effect was most apparent within the highest decile categories of SBP level.

Figure 6.16: Incidence of Ischemic Heart Disease after age 50 years by decile of Systolic Blood Pressure level and Systolic Blood Pressure trend



6.5.3 Modeling aspects of tracking and Ischemic Heart Disease

The three indicators of aspects of tracking, level, trend and variability, defining SBP, DBP and BMI patterns for each subject were modeled as possible additional risk factors for IHD. Level was modeled as a continuous variable, scaled in units of 10 percentiles. Trend was categorized in tertiles, with the middle tertile, subjects with flat trends defining the reference category. Variability was defined as high or low (reference category), based on values above or below the median of the distribution of root mean square error values.

Three Cox proportional hazard models were fit based on measurements at age 50, 60 and 70 years. Each base Cox model included year of examination, smoking, DM, BMI%ile and the BP percentile (either SBP%ile or DBP%ile) at the examination. Four variables describing level (1 continuous variable), trend (2 categories and reference) and variability (1 category and reference) for each risk factor were added to base models. Separate models at each age were fit to examine the contribution of SBP, DBP and BMI tracking.

As shown in Table 6.32, when added to the Cox proportional hazard model at age 50 years for IHD; SBP level and SBP trend were statistically significant in addition to SBP%ile at age 50 years that remained significant in the model. A difference in 10 units in "SBP level", the average percentiles of past SBP measurements, reflected a 9% (95% CI 4%,15%) increased risk of IHD. Those in the top tertile of all slope measurements at age 50, that is, those with positive slope, relative to those with a flat slope, incurred an

increased risk of IHD of 23% (95% CI 3%,46%). Also, examined separately, DBP level added significantly to the model at age 50 years, as did BMI level and BMI variability. The level variable entered the model in addition to, not replacing, the percentile value of the variable that remained significant in the model. Subjects with high variability in the slope of BMI measurements with age up to 50 years, i.e. variability above the median value, had a 25% (95% CI 8%,45%) increased risk of IHD, relative to those with variability in their slope below the median of all values.

At age 60 and 70 years, level of SBP and level of DBP each contributed significantly to models in addition to the percentile value of these variables in models at these ages. This indicates the value for prior BP measurements in addition to the BP measurement at these ages for models of IHD. BMI level contributed to the model at age 60 years, but not at age 70 years. For all three risk factors, trend and variability were not significant in models at age 60 or 70 years, when considered with level.

Table 6.32 Adjusted Relative Risk, with 95% confidence intervals, of Ischemic Heart Disease for measures of tracking for Systolic Blood Pressure, Diastolic Blood Pressure and Body Mass Index at age 50, 60 and 70 years.

Risk Factor	Tracking Variable	Age 50	Age 60	Age 70
SBP	LEVEL	1.09	1.12	1.18
	(10 %iles)	1.04,1.15	1.06,1.19	1.06,1.31
	TREND	1.08	1.15	0.90
	(negative vs flat)	0.90,1.30	0.92,1.44	0.56,1.45
	TREND	1.23	1.19	0.87
	(positive vs flat)	1.03,1.46	0.96,1.47	0.59,1.28
	VARIABILITY	1.00	1.16	1.31
	(high vs low)	0.86,1.15	0.97,1.37	0.96,1.81
DBP	LEVEL	1.12	1.11	1.20
	(10 %iles)	1.06,1.17	1.02,1.21	1.08,1.34
	TREND	1.00	0.56	1.16
	(negative vs flat)	0.83.1.19	0.29,1.10	0.76,1.76
	TREND	1.01	0.70	1.00
	(positive vs flat)	0.84,1.21	0.35,1.37	0.68,1.47
	VARIABILITY	0.88	0.94	0.90
	(high vs low)	0.76,1.02	0.79,1.12	0.65,1.24
BMI	LEVEL	1.05	1.03	1.06
	(10 %iles)	1.02,1.08	1.00,1.07	0.99,1.13
	TREND	1.05	1.04	0.79
	(negative vs flat)	0.88,1.26	0.83,1.29	0.51,1.21
	TREND	1.02	1.03	1.23
	(positive vs flat)	0.86,1.22	0.84,1.28	0.86,1.76
	VARIABILITY	1.25	1.08	1.04
	(high vs low)	1.08,1.45	0.89,1.30	0.74,1.44

At each age LEVEL, TREND and VARIABILITY were added to models including year of examination, DM, smoking and either SBP%ile or DBP%ile.

7 DISCUSSION

Now in its fifty-first year, the Manitoba Follow-up Study continues as the prospective cohort study, conceived, designed and executed by Dr. Francis A. L. Mathewson. His cohort consisted primarily of young men who had been found fit for air crew training by the RCAF during WWII. These men had served their country, survived the war, and were invited to participate in a long term investigation of cardiovascular disease. Since then, throughout their adult lives, these men have faithfully responded to annual contact and periodic requests for medical examination. The high rate of completion of routine examinations and the evolution of a highly successful follow-up protocol for maintaining contact with study members has resulted in the development of database with medical information spanning the lives of these men before development of disease, during the process of disease development and following disease onset. The success of the MFUS reflects the dedication and perseverance of Dr. Mathewson and the outstanding contribution of the 3,983 men.

7.1 Summary of key results

The epidemiology of IHD over a 45-year observation period in the MFUS cohort of 3983 men has been described. Incidence of IHD, distribution of risk factors and the

relationship between the two over time were examined through five specific objectives in this thesis. This section provides a summary of the key findings of this analysis.

Twenty eight percent of the cohort, 1098 men, developed evidence of AP, MI or SD between 1948 to 1993. The incidence of IHD increased with age. Four cases were diagnosed between 30 and 34 years of age. At that age, the incidence was low, less that 1 per 1000 pyrs. Incidence increased almost linearly, so that by age 75-79 years 17 first IHD events per 1,000 pyrs were occurring. The incidence of AP and MI were similar up to age 65 years, where after MI incidence continued to increase and AP incidence plateaued. SD incidence increased with age and was lower than the incidence of either AP or MI at every age.

Systolic and diastolic blood pressure, body mass index, diabetes mellitus and smoking are recognised IHD risk factors. The distributions of these risk factors over time were shown to vary with age and period of time measured. Levels of SBP and DBP, tended to increase with age to 60 years, SBP continued to increase and DBP plateaued there after. The variability of blood pressure, more so for SBP than DBP, also increased with age. BMI increased with age, and levelled off at age 60 years with a mean about 1.5 kg/m^2 lower than reported for the Canadian male population at comparable ages. More than 50% of the MFUS cohort smoked during the early years of the study. The proportion of current smokers declined with age and time to rates comparable to the rest of the Canadian population (Stachenko 1992). Prevalence of diabetes increased with age

to about 9 percent by age 75 years. In general, distributions of all risk factors were changing with age.

Utilising the longitudinal nature of repeated routine measurements of subjects, at 5-year intervals, between 30 and 75 years of age, strong evidence for tracking of SBP, DBP and BMI was established by two methods. Correlation coefficients between serial measurements of SBP, DBP and BMI and the relative likelihood of a measurement remaining in the top or bottom quintiles of these distributions on repeat measurement were calculated. The evidence for blood pressure tracking was greatest at 5-year intervals in subjects between 30 and 50 years of age. From the same age, and over the same interval of time, with either index of tracking, evidence for tracking of BMI was stronger than that for either BP.

The significance of the effect of a risk factor for IHD may vary for different clinical manifestation of IHD. The possibility of this was explored in this thesis. In general, in multivariate models, DBP was stronger than SBP for AP and MI. SBP rather than DBP was more strongly associated with SD. BMI was important in models of AP and SD, but only significant at age 40 for MI. DM was consistently associated with MI at ages 50 through 65 years, and at ages 55 and 65 years for SD, but in general not for AP. The relative risk for smoking in models was significant in multivariate models of MI up to age 50, at younger ages, 35 and 40 years for AP, and at 40 and 55 years for SD.

As well, the relative risk of IHD and its manifestations for some risk factors declined significantly with age. Relative risk for blood pressure declined with age overall

for IHD and for AP. The effect of DBP significantly declined for MI. The effects of neither SBP nor DBP significantly declined with age for SD. Even though the relative risk associated with BMI for IHD and its manifestations appeared stronger both in magnitude and statistical significance at younger compared to older ages, the effect of BMI did not significantly change with age, and when its effect was estimated over all ages for SD, was not statistically significant. The relative risk of DM for IHD and its manifestations in models from age 50 years and older did not significantly change with age. The effect of smoking declined with age for IHD, MI and SD. Over all ages, smoking was not significant in models for AP.

Evidence for tracking of blood pressure and BMI was established. This lead to a characterisation of tracking at the individual level, based on a description of the linear relationship between prior blood pressure and BMI measurements and age. Level, trend and variability were used as indicators of individual tracking patterns of risk factors over time. These indicators derived from prior repeat measurements of blood pressure and BMI before ages 50, 60 and 70 years, significantly contributed to models of IHD. The contribution of the tracking indicators to models of IHD was in addition to the contribution of measurements at that point in time.

7.2 The Design and Conduct of the Manitoba Follow-up Study

The Manitoba Follow-up Study ranks worldwide with few other medical research projects ever undertaken in scope, duration and detail of the investigation of the natural

history of ischemic heart disease. By design the MFUS has prospectively documented the medical histories of 3,983 originally healthy, young men for more than 50 years. Most of these men left the RCAF at the end of WWII to embark on new careers. Many remained involved in aviation, some moved to civilian occupations and others returned to school. The emphasis of the MFUS has been on the detection of electrocardiographic abnormalities and routine assessment of selected ischemic heart disease risk factors, to aid in the prediction of CVD. A medical database has been developed to include information collected before disease onset, recorded details at the time of diagnosis of disease, and documentation of the prognosis of individuals following disease.

7.2.1 Unique aspects of the Manitoba Follow-up Study

The MFUS is unparalleled in Canadian medical research. Many aspects of this study are truly unique and merit elaboration. Some questions arise with the longevity of any project, but perhaps even more questions arise with a study of this magnitude. Factors that are associated with the maintenance of a cohort during a longitudinal study include a stable and flexible staff that communicates well with the subjects, the development of a collaborative effort or "subject bond" between the researcher and participants and the perceived importance of the study by the participants (Marmor et al. 1991).

Reasons for the completeness of the records lie in part with the nature of the cohort at the beginning of the MFUS as well as with the dedication of Dr. Mathewson and his staff. An understanding of one study member's perception for his own contribution to and reasons for uninterrupted involvement in the MFUS may further enlighten the

reasons behind the success of the follow-up program. It is possible through qualitative methods, using a life history interview with partially directed questions, to obtain some insight into his perception. To explore this issue, a study member living in Winnipeg, whom I had not previously` met, agreed three years ago to my request to a video taped interview to discuss MFUS. Part of that 90 minute interview explored the question of why someone would continue to be part of a study for this long, and why someone would bother to keep getting examined and send back questionnaires? Segments of that interview are as follows:

About 15 minutes into the interview I asked: "... by the early 1960's the first reports were being published. You perhaps weren't aware that these results were being reported, or were you?"

The study member responded "We didn't know exactly what the results were being acquired or exactly how they were being used, but uh, seeing you were dealing with something with the individual, as long as the individual was healthy it wasn't making any difference in his eyes. (I said, "That's right") It's the same thing with other body organs and anything else, if we can contribute to other people it's something we should do in my view and it's obvious that connected to the University it was not a commercial operation and nobody was marketing this in the ordinary sense of marketing and if advice and statistics were helping other people, that was good."

I later asked: "Can you tell me why after close to fifty years, you would still even be interested in sending anything back to us? Why have you stayed involved with this study for this long?"

He responded: "Well uh, I think now at this late date it's really a case of stubbornness. When you've been involved in something for a long, long time particularly with military experience where in a lot of cases survival is something you have to believe in, there is just a general interest in the survival of the group that I'm a part of, interested in and to see just really how we do in many ways later in life. And the fact that there is a very strong possibility that it's maybe going to really bear fruit and help future generations, it is something that certainly has my support."

Near the end of the interview I said: "Are there any parts of this (Study) that you're a little more curious about, now that I've talked on and on about some things."

He replied: "No, the essence of it from my point of view would be, and I think it would be popular from the rest of the group, is the hope that you'll hold out for applying this to younger people. That an electrocardiogram may be recorded down the line somewhere and through this Study a Doctor will say: 'Well we think this leads to this and because of that we are going to do something about it.'"

These interview segments all seem to have a common thread linking this study member's ideas of commitment for the betterment of mankind from his experience during WWII and throughout his involvement with the MFUS. This study member has been

responding to the requests of the study not for his own personal health benefits, but rather, he has conveyed his very serious and sincere desire to help mankind and future generations through his participation. Early in the interview he told me that his enlistment in the RCAF came from a sense of responsibility to protect the citizens of Canada and a sense of perhaps doing what was necessary and expected, really without any motivation for personal gain or reward. I see an underlying theme of nationalism, and a sense of unselfish devotion to mankind from his responses. I feel that his involvement with this study continues because of his belief that MFUS may help prevention of cardiovascular disease in future generations.

7.2.2 Strengths, weaknesses and generalizability of the Manitoba Follow-up Study

The young age and narrow age range of the MFUS cohort at entry coupled with the long duration of follow-up has resulted in the opportunity to document all incident events of cardiovascular disease from a mean age of 30 years, up to about 75 years of age. The documentation of IHD as it developed was possible through the routine examination of study members with recordings of electrocardiograms to aid diagnosis of some otherwise undetectable types of MI. The design, data collection protocol and duration of follow-up are all strengths of the MFUS that have enhanced the documentation of incident IHD.

The ascertainment of vital status by the end of the 45-year follow-up period was obtained for 96 percent of the cohort. The frequency of missing 5-year birth anniversary examinations was low, 6.4 percent of the possible selected examinations. This minimized

problems all longitudinal studies face with interpretation of results based on less complete follow-up and less complete medical data.

A more selective nature for recruitment of RCAF air crew, compared to both recruitment to other branches of the armed forces and compared to men not recruited to serve during WWII may have resulted in healthier or more elite subjects entering the MFUS cohort compared to the general population. Air crew recruits were excluded on the basis of evidence for clinical disease. This selection process may hinder the generalizability of the study's results to the Canadian male population. Some cohort members were found not fit for pilot training and were considered for other air crew or ground crew training. Pilots may have had better cardiovascular profiles at entry to the study, compared to those who had served in other capacities (Tate, in progress). About half of study members remained involved with aviation throughout their adult lives, with about half of these, 25% of the cohort, being career pilots. However, many study members returned to civilian occupations at the end of the war.

During the course of follow-up, study members were in all strata of society, although the majority or non-aviation occupations were in "white collar" positions. If the structure of the MFUS cohort is such that the members were somewhat healthier at entry and in higher social positioned environments than the general population then, to some degree, the potentially confounding effects of socioeconomic characteristics with cardiovascular disease, often difficult to define and often more difficult to measure, may

have been controlled to some extent through the more homogeneous composition of the cohort.

The MFUS is a prospective study of disease as it developed in a free living cohort. The majority of the study members are now retired, most live in Canada, but some are scattered all over the world. Within Canada, many study members have found southern Ontario or British Columbia favourite retirement communities, as have many other Canadian seniors. A sizeable number (perhaps the hardy ones), live in Winnipeg, where the study has been housed since its inception. Each man visits his personal physician, and consequently some concern may be expressed about the standardization of measurements, consistency and completeness of reporting. However, with the geographic diversity of the cohort, a reasonable representation of the Canadian elderly male population and the health care they receive across Canada can be inferred.

Details of the frequency of prescription and compliance to pharmaceuticals for treatment of hypertension have not been recorded in this study. All that has been recorded is type of medication and date of prescription. Hence, the ability to address effects of antihypertentive treatment on level of blood pressure is clearly limitation of this study. This limitation was addressed in the previous published analysis of tracking (Tate 1995b) where it was shown that only 3% of the cohort had been prescribed any antihypertensive medication before age 50 years. Further, it was mentioned that at age 65 years and older, at least two-thirds of those on treatment were still found in one of the top two quintiles of the blood pressure distributions. Thus treatment of blood pressure may

have only a marginal effect on measures of tracking. In this thesis, the blood pressure measurements in men between 30 and 50 years of age showed strong evidence for tracking as well a strong predictive value for incidence of IHD. Most of the measurements through this age range would have been recorded during the first 20 years of the study. During this period of time external effects on risk factor patterns, such as antihypertensive treatment on blood pressure levels, would have been small. The effect of treatment on blood pressure levels has not been addressed in modeling incidence of IHD.

The mortality experience of the MFUS cohort has remained low relative to the mortality of the Canadian male population over the same years of observation. This may in part be a result of the healthier nature of the cohort at entry to the study. Further, the lower mortality experience may reflect the value of routine examinations, enhancing the opportunity to detect disease at earlier stages. None the less, the distribution of cause of death in the MFUS, apart from death due to aircraft accidents, has been similar to the Canadian experience when compared at a midpoint, 1984, of time under study.

This is a study of cardiovascular disease in men, only. Cautions have been expressed, in the past, concerning the generalisation of the MFUS results to female populations. The age-specific incidence of CHD morbidity and CHD mortality are well recognised to be greater in men than in women, with CHD mortality rates for women approximately equal to the rates of men about 10 years younger (Pagley and Goldberg 1995). Despite the huge geographic variation in CHD rates, this two to three fold age-

specific male to female excess has been reported world wide (Khaw 1992). However, the effect of main risk factors, blood pressure, smoking and cholesterol have all been found to be important in both genders (Meilahn et al. 1995), and with about the same relative magnitude (Lerner and Kannel 1986). One exception is the effect of diabetes. While the reasons for a differential effect is uncertain, the relative risk of CHD has been reported to be much greater for females than for males with DM (Barrett-Connor and Wingard 1983). It would still appear reasonable to speculate that the results of the MFUS analysis relating the value of risk factors with age and the extent of tracking of risk factors could be extended to females.

While electrocardiograms and measurements of blood pressure and BMI are routinely obtained, other areas of data collection are lacking. Routine medical requests did not include any collection of blood lipid measurements. In the mid 1960s, Dr. Mathewson approached Health and Welfare Canada with a request for funding to systematically obtain cholesterol measurements from the subjects, but was unsuccessful. Hence, while serum cholesterol and its components have been studied by others and found to be major risk factors for CHD, no analysis of this is possible in MFUS. Smoking data is based on reply to either two questionnaires, from 1974 and 1982, and a chart review of the non responders at that time. Smoking data is unavailable for 14% of subjects, and no smoking data has been updated since that time. It is unlikely that many non-smokers would have started smoking after 1982. However, smokers in 1982 may have later quit, and would be

misclassified as current smokers at older ages in this analysis. Diagnosis of diabetes mellitus is based on self-report by the study member or reported by his physician.

The number of subjects who contributed examinations at the 5-year birth anniversaries between ages 35 and 65 years varied between 2,447 and 3,515. This number of subjects ensured a high statistical power to detect significant effects of risk factors at these ages. At age 70 and 75 years, the number of subjects with examinations was fewer. Hence, the power to detect significant effects of risk factors was reduced. The MFUS is ongoing. Data continues to be collected from the study members, now at a mean age close to 80 years. In the future, an analysis of risk factor effects in the very elderly may be possible.

7.3 Comparison of results to other studies

7.3.1 Incidence of Ischemic Heart Disease

While CHD mortality rates are readily available from many sources, there are very few population reports describing incidence of IHD morbidity. A reason for this lies with a recognition, understanding and appreciation for the data necessary to calculate incidence of disease. A cohort of disease free people must be assembled and followed prospectively with repeated examination to document first evidence of IHD. The cohort must be followed through age ranges where IHD events are likely to occur. As well, the cohort must be followed long enough for IHD events to accrue. This is not an easy task. Issues surrounding unsuccessful attempts to establish an IHD incidence registry in

Canada have been reviewed (Wielgosz 1992). Mortality records from vital statistics offices documenting cause of death are much more easily obtained and consequently cardiovascular mortality rates from populations are more frequently reported.

Incidence of IHD in the MFUS increased with age from 1 per 1,000 pyrs before age 40, to 17 per 1,000 pyrs by age 75-79 years. IHD incidence in the United States has been estimated by the Pooling Project (The Pooling Project Research Group 1978) on the basis of the 10-year experience of a total of 12,516 middle aged men. The incidence of first major coronary event was similar at ages 40 to 49 years to that estimated in the MFUS, but higher incidence rates than in the MFUS were reported after age 50 years. After 26 years of follow-up, the Framingham study reported 1240 incident CHD events, between ages 35 and 84 years, in the men and women of their cohort (Lerner and Kannel 1986). Annual incidence of CHD per 1,000 pyrs in age decades for the Framingham men was reported to be 4.1 (age 35-44), 10.8 (age 45-54), 20.1 (age 55-64), 22.5 (age 65-74) and 25.2 (age 75-84), a gradient similar, but with rates greater than those in the MFUS cohort. In the Framingham study men, 43% presented with MI, with another 13% as MI with AP coincident. AP without MI presented in 35% of cases and 10% as SD alone. After 30 years of follow-up (Kannel and Vokonas 1992) the Framingham study reported that MI was the dominant manifestation of IHD after age 65 years, and that the proportion of subjects with SD as first manifestation of IHD increased with age, to about 20% after age 75 years. This is similar to the distribution of the three manifestations of IHD in the MFUS where almost half (47%) of incident IHD events were MI. As in the MFUS

cohort, the Framingham study reported that the incidence of AP leveled off at about 10 per 1,000 pyrs after age 55 years (Kannel and Feinleib 1972). In another Canadian study, of 4,576 men in rural Quebec (Dagenais et al. 1990b) the reported incidence of AP increased with age from 3 per 1,000 pyrs at age 35-44 to 6 per 1,000 pyrs at age 45-54, and levelled off at age 55-64 years at about 10 per 1,000 pyrs. Consistent with the findings in the MFUS, the Quebec study incidence of MI continued to increase with age after 65 years. In a Finnish study of over 10,000 middle aged men and women, 30-59 years of age at entry, after a follow-up interval of 5.5 years, the incidence of MI in men age 30-39 was 2.9 per 1,000 pyrs, at age 40-49 was 7.3 per 1,000 pyrs and at age 50-59 was 14.1 per 1,000 pyrs (Reunanen et al. 1985). The incidence of "new angina" at the same ages in men was 3.7, 7.6 and 13.1 per 1,000 pyrs, respectively. The Copenhagen City Heart Study (Nyboe et al. 1989) of 5,923 men 40 - 69 years of age followed over an average of 6.5 years was designed to specifically evaluate the incidence and risk factors for MI. The Copenhagen Study reported the incidence of MI to increase with age from 0.0 at age 35-39, 1.8 (age 40-44), 3.2 (age 45-49), 5.2 (age 50-54), 8.0 (age 55-59), 10.0 (age 60-64), 13.6 (age 65-69), 11.1 (age 70-74), and 11.7 (age 75-79) per 1000 pyrs. The Copenhagen Study documented evidence of MI based on self report of symptoms followed for confirmation by contact with physicians. The rates of MI they report are lower than those of MFUS. Their approach would have undercounted MI by excluding "silent MI" and possibly overcounting events by including those with prior AP and

possibly counting prevalent MI at entry. The relationship of increasing incidence of MI with age is in keeping with that of the MFUS.

Some researchers have relied on administrative health records and have used hospital discharge records to estimate incidence of IHD. While useful for hospital planning, this approach is fraught with difficulty as a suitable means of estimating incidence of disease. For example, only cases reporting to hospital are recorded. It has been estimated that as many as 25% of MIs may be clinically "silent", and be detected only with an electrocardiogram (Kannel and Abbott 1984). In MFUS, about 20% of MIs were clinically "silent". In Canada, a study of mortality statistics and hospital separation rates for a period from 1976 to 1991, estimated rates of MI per 1000 population in men to range from 0.3-0.4 at ages under 45 years, 5.6-7.6 for ages 45 to 64 years, and 14.2-15.2 in men over age 65 years (Brophy 1997). Again, these rates apply only to men with a diagnosis of MI on a hospital record, and hence, will include re-infarction as well as incident MI events. As well, this includes men with prior AP. So while reported rates may be thought to represent incident MI, these rates do not represent incident IHD events. A Canadian report of trends in morbidity and mortality rates of MI using administrative data from Nova Scotia and Saskatchewan between 1977 and 1985 presented an age adjusted rate of first MI for men 25 through 74 years of age to range from 4.4 to 7.0 per 1,000 pyrs (The Nova Scotia-Saskatchewan Cardiovascular Disease Epidemiology Group 1992). The incidence of "uncomplicated" SD in Framingham males, based on death within one hour of onset of symptoms in men without prior evidence of CHD, was

reported as 1.59 per 1,000 pyrs after 26 years of follow-up (Schatzkin et al. 1984). This figure is difficult to compare with MFUS because of differences in definition of SD.

Because IHD events were documented through the follow-up period by routine examination of disease free subjects from entry to the study, the MFUS estimate of the incidence of manifestations of IHD in Canadian males should be considered the most comprehensive and accurate available.

7.3.2 Risk factor distributions

As part of the Canadian Heart Health Initiative (Health Promotion Directorate 1992), the Canadian Heart Health Survey consisted of a series of cross sectional surveys of Canadian adults carried out in each province in the late 1980s and early 1990s (MacLean et al. 1992). The age-specific mean and standard deviations of SBP and DBP in the MFUS cohort were similar to those measured during the personal interview conducted in 10,110 males as part of that survey (Joffres et al. 1992). Mean blood pressure in the MFUS also parallel that reported for US males in the National Health and Nutrition Examination Survey (NHANES) where SBP was reported to increase with age and DBP to increase to age 50-59 years and decrease after that age (Burt et al. 1995). Means and standard deviations of age-specific BMI measurements in the MFUS cohort were consistently 1.5 kg/m^2 lower than those reported in the same cross sectional survey of the 8,796 males who also attended the laboratory component of the survey (Reeder et al. 1992). So although mean blood pressure was similar, the lower mean BMI suggests that MFUS subjects may be somewhat fitter than their Canadian peers. In a Framingham

report over a 36 year follow-up, a 20 mm Hg increase in SBP and a 10 mm Hg increase in DBP over the ages 30 though 65 years was found (Kannel 1996). Risk factor levels of Framingham males over age 65 years were reported in 5-year intervals (Larson 1995). A mean BMI of 26.1 kg/m^2 at age 65-69 began to decline with age. Similarly, mean SBP of 140 mm Hg at this age declined to 134 mm Hg by age 80-84 years, although based on only 40 men at that age in their cohort.

There were no diabetics in the MFUS cohort at entry. In contrast, 1.92% of the Framingham cohort had DM at entry to that study (Dawber 1980). The age-specific rates of DM in the MFUS cohort are similar to rates reported by others in North America. Between 1980 and 1987 the prevalence of diabetes for United States white males ranges from 4.3 percent to 6.5 percent in men age 45-64 years (United States Department of Health and Human Services 1990). Prevalence of DM among Canadian community dwelling elders was 10.2% (age 65-74 years), 9.8% (age 75-84 years) and 7.8% (age 85 years or older), as reported by the Canadian Study of Health and Aging (Rockwood et al. 1998).

Over half of the MFUS members before age 50 years smoked. The percentage of smokers in this cohort decreased with age to about 25 percent by age 70 years. These smoking rates were similar to those reported during the same period of time by the Pooling Project, 44 percent at age 50-54 and 37 percent at age 55-59 (The Pooling Project Research Group 1978). In the late 1980's the prevalence of smoking in Canada was estimated to be 40 percent in males age 35-44 years, decreasing to 23 percent by age 65

to 74 years (Stachenko et al. 1992). The MFUS smoking data represent age-specific prevalence estimates of smoking habits in men over a 45-year period. The majority of examinations at age 30 through age 50 years would have been recorded during the 1950's and 1960's, a period of time when Canadian smoking rates were markedly higher than today.

7.3.3 Tracking of Blood Pressure and Body Mass Index

Successive measurements of the same biological parameter in an individual over time may be predictable to some extent. Tracking describes the extent of predictability or relative constancy that a measurable continuous scaled characteristic may have in a group of individuals over time with repeated observation. The mathematical and analytical aspects of tracking have been recently reviewed (Twisk et al. 1994). There is no single comprehensive definition of tracking. Based on the repeat measurement of a biological parameter, evidence for tracking exists if an individual maintains his ranking relative to others in a population over a specified time period (Foulkes and Davis 1981), or where the expected value of the relative deviation of an individual's value from the population mean remains unchanged over time (McMahon 1981), or when measurements from an individual over time show systematic change that facilitates prediction of future values (Ware and Wu 1981). These definitions require an examination of patterns of individual measurements, of all subjects, over the entire range of measurement values, over periods of time.

Two indices of tracking were used in this analysis. The serial correlation coefficient expresses the strength of a linear relationship between measurements over time. In this analysis, the entire ranges of SBP, DBP and BMI were examined at 5-year examinations using correlation analysis. In the relative likelihood approach to tracking, subjects are classified at repeat measurement over time using cut points of distributions. The relative likelihood approach was used to focus on the subjects with measurements at the extremes of the SBP, DBP and BMI distributions (Twisk et al. 1994). In this thesis, an adjustment was incorporated into the calculation of the relative likelihood measure, to compensate for the imprecision of the process to determine exactly 20% of observations in the top or bottom quintile of the distribution of measurements.

Tracking of blood pressure and cholesterol measurements in children has recently been reviewed (Labarthe et al. 1991) and tracking of blood pressure from youth to early adulthood (Nelson et al. 1992, Beckett et al. 1992) has been reported. There have been few reports regarding tracking of blood pressure from early adulthood to middle and older age (Mathewson et al. 1972, Rosner et al. 1977, Rabkin et al. 1982, Tate et al. 1995b). Since the investigation of the degree of tracking of a biological parameter over varying ages and time intervals requires a large source of longitudinal data, studies like the MFUS and the Framingham Study provide excellent opportunities to examine tracking of adult male blood pressure and body build.

Elevated blood pressure in middle age is widely accepted as a major risk factor for subsequent cardiovascular complications such as CHD and stroke (Rabkin et al. 1978a,

The Pooling Project Research Group 1978, Rabkin et al. 1979, Dawber 1980). Consequently, identification of young adults who are likely to maintain elevated blood pressure in later life should be of prime importance in preventive medicine.

Analysis of the MFUS cohort, showed that mean SBP and its variability increased steadily between age 25 and 75 years. The relationship of blood pressure to subsequent cardiovascular complications is likely best described as a continuum of risk (MacMahon et al. 1990) whose effect may change with age. With this premise, it is important to recognise that there may not be one fixed cut point of blood pressure defining a level beyond which there is an increased risk applicable to individuals of all ages. Because of this, the concept of tracking blood pressure is important. If men in the upper end of the blood pressure distribution have the greatest likelihood to remain at high levels relative to others of the same age, then men at the highest risk of cardiovascular disease in later life can be identified at a young age, before their blood pressure is sufficiently elevated to satisfy traditional definitions of hypertension. This analysis provides supporting evidence that tracking of blood pressure does exist from young adulthood. At both the top and bottom ends of the systolic and diastolic blood pressure distributions subjects tended to stay in their respective end of the distribution, for intervals up to 30 years.

The strongest evidence of blood pressure tracking, found by both methodological approaches, was for middle aged men. This is consistent with other reports (Rosner et al. 1977). Weaker tracking of SBP in adults at younger ages in the MFUS cohort has been previously reported (Rabkin et al. 1982). Others have reported correlation coefficients

ranging from 0.3 to 0.4 in young adults up to age 20 years, over a 9-year interval (Kemper et al. 1990). This group also reported the "relative probability" of staying in the top quartile of the blood pressure distribution over 9 years to be 2.0 for DBP and 3.0 for SBP. The probability for men in the high-normal range of DBP (85-89 mm Hg) to develop hypertension was 2.25 times greater than in those with normal DBP (Leitschuh et al. 1991). Stronger evidence for tracking was found for shorter, in contrast to longer, intervals of time between measurements in the MFUS analysis.

Because hypertension is a known and potent risk factor for IHD, elimination of individuals from analysis after development of IHD may result in a weaker degree of tracking of blood pressure at older ages. With the MFUS data, it is not possible to evaluate specific medications and compliance to antihypertensive treatment. Based on previous analysis of MFUS data, antihypertensive treatment seems to have had little effect on the degree of tracking of blood pressure. While antihypertensive treatment may lower the absolute level of blood pressure, the majority of the men to whom treatment was prescribed tend to remain in the top quintile (Rabkin et al. 1982, Tate et al. 1995b).

Digit preference in recording SBP and DBP posed some difficulty when identifying quintiles in that it was not always possible to identify exactly 20% of subjects. At some ages, many subjects had a blood pressure reading recorded at one value. For example, at age 45 years, 25 percent of DBP measurements were recorded as 80 mm Hg. At this age, however, subjects with this DBP reading were not classified into either the top or bottom quintile. At most ages, close to 20 percent of measurements could be

identified for both the top and bottom quintiles. This does not hamper the calculation of the relative likelihood measure, as the method does not require identification of exactly 20 percent of measurements.

There was strong evidence for tracking of BMI in this analysis. Correlation coefficients for pairs of measurements at all ages were greater for BMI than for either SBP or DBP. Relative likelihood measures for BMI were also considerably greater than for either blood pressure measurement, with subjects in the top quintile of distributions at younger ages being at least three times as likely to remain in the top quintile on later measurement. One explanation of the value of obesity as a predictor of CHD is that the metabolic complications of excess weight may require a long period of time before an effect can be observed (Williams et al. 1997). This explanation is consistent with strong evidence for tracking of BMI and its constant effect from young ages in models of IHD. Previous analysis of the MFUS reported that overweight young men were at greater risk over the long term for IHD (Rabkin et al. 1977).

7.3.4 Risk factor effects for Ischemic Heart Disease

7.3.4.1 Declining effect of risk factors with age

In the MFUS, IHD was found to develop in men at a young, middle or older age. With aging, both the distribution of risk factors and the incidence of IHD change (Fried et al. 1991). Hence, the relative risk of IHD associated with a specific factor may also vary with age (Tate et al. 1998). The MFUS cohort presented a unique opportunity to study the changing effect of risk factors for IHD with age. An objective of this analysis was to

determine the age-specific relationships between risk factors at ages 30 to 75 years and incidence of IHD and to determine the effects of aging on these relationships.

A recent review of nine studies (Kornitzer and Goldberg 1991) concluded that there is little doubt that serum cholesterol, blood pressure, cigarette smoking and diabetes are predictors of long term coronary heart disease incidence and mortality. The question was raised as to whether the risk factors for IHD identified at a young age are still predictive at older ages. It was emphasised that only with long term studies can questions concerning the changing effect of risk factors with age be addressed. This question has been addressed in this thesis. It was found that while the effects of DM and BMI did not vary, the relative risk of IHD associated with both smoking and blood pressure decreased significantly with age.

The MFUS finding with respect to the declining effect of smoking with age on risk of IHD is consistent with several other studies. In the Framingham Study (Kannel and Larson 1993) a significant risk for initial CHD events was found for men 35-64 years but not for men 65-94 years of age. The Pooling Project (The Pooling Project Research Group 1978) reported that in men between 40 and 64 years, the relative risks for smoking were higher for younger compared to older men. In a study of 50-year-old Swedish men (Welin et al. 1993), smoking was significant in the first 15 years, but not the last 10 years of a 25 year follow-up period. In the Honolulu Heart Program (Benfante et al. 1989, Benfante et al. 1992), a greater relative risk for smoking was found for CHD onset prior to age 60 years than for onset after age 60 years. While there is no clear explanation for

the reduction of relative risk in the elderly, it may be that susceptible smokers have stopped smoking or that there is an increased mortality among smokers at younger ages. The United States Surgeon General's report summarised the results of several population studies of smoking and cardiovascular mortality (United States Department of Health and Human Services 1983) and concluded that the relative effect of smoking declined in the elderly. Rising cardiovascular mortality rates in non-smokers at more advanced ages may play a role in the declining relative effect of smoking (United States Department of Health and Human Services 1983).

Studies are less consistent with respect to blood pressure and aging. In this MFUS analysis, blood pressure up to age 65 years, either SBP or DBP, was a significant risk factor for IHD. Also, the age-specific relative risk associated with a 10 mm Hg difference in blood pressure declined significantly with age. Consistent with MFUS, the Framingham Study reported a significant risk for initial coronary heart disease events associated with high blood pressure in each sub-group of younger men, age 35-64 years, and older men, 65-94 years (Kannel and Larson 1993) and that the risk ratio for high blood pressure in the older men had declined. Unlike the findings of MFUS, the Pooling Project (The Pooling Project Research Group 1978) reported a positive slope of SBP with incidence of coronary heart disease that did not decrease with age between 40 and 64 years. In the Swedish study of 50 year old men (Welin et al. 1993), SBP was predictive of MI or fatal CHD independent of duration of follow-up period. In the Honolulu Heart Program (Benfante et al. 1989, Benfante et al. 1992), SBP was associated with CHD in

both younger (under age 60 years) and older (over age 60 years) men. In this MFUS analysis, the absolute risk of IHD, i.e. the incidence, increased with age and was highest in the elderly. The fewer number of subjects at risk of IHD and the increased variability of blood pressure measurements at older ages may have influenced the level of significance of relative risk estimates. Reduced relative risk estimates in our study do not necessarily imply that blood pressure level is unimportant in the elderly. Treatment of isolated systolic hypertension in the elderly (SHEP Cooperative Research Group 1991) has been shown to be beneficial in reducing the rate of coronary heart disease through the lowering of high SBP levels.

MFUS results from Cox PH modeling suggested that the risk ratio for a 10 mm Hg lower blood pressure was smaller in older compared to younger men. Further, the risk difference in IHD incidence between men in the top and bottom blood pressure quintiles continued to widen with advancing age. However, while the risk ratio was based on the same constant difference at each age, the difference in blood pressure level between the top and bottom quintile increased with age.

The difference between SBP and DBP is called pulse pressure. The finding of increased mean levels SBP after age 60 years while at the same ages mean DBP levelled off suggests that pulse pressure would be increasing at older ages. Hence, pulse pressure may be an important variable to consider in the elderly. Pulse pressure has been investigated with Framingham data (Franklin et al. 1997) as well as in a large scale

French study of 19,083 men age 40 to 69 years, where wide pulse pressure was predictive of CHD mortality (Benetos et al. 1997).

The effect of BMI on risk of IHD did not vary significantly with age and hence was an important risk factor from age 30 years. This has been previously reported in the MFUS cohort (Rabkin et al. 1977, Rabkin et al. 1979). In contrast to these findings, the Pooling Project (The Pooling Project Research Group 1978) reported a greater relative risks for relative weight in younger compared to older men. In the Swedish study (Welin et al. 1993) BMI was not significant in either period, that is, not in the first 15 years nor the last 10 years of follow-up. In younger men, under age 45 years, overweight men, defined as BMI above 25.5 kg/m^2 had greater mean values of BP, total cholesterol, triglycerides and glucose, while no difference was reported in men over age 45 years (Egan et al. 1991). DM was most strongly associated with risk of IHD in MFUS subjects between age 50 and 65 years. The Framingham Study (Kannel and Larsen 1993) reported a significant risk for initial coronary heart disease events associated with DM at all ages. In the Honolulu Heart Program (Benfante et al. 1989, Benfante et al. 1992), a greater relative risk for coronary heart disease was associated with serum glucose level at all ages and with BMI in younger men.

7.3.4.2 Varying effect of risk factors for different manifestations of Ischemic Heart Disease

Analyses of the effect of risk factors for the specific manifestations of IHD; AP, MI and SD have been reported infrequently. In the MFUS analysis, blood pressure was

an important independent predictor of AP to age 65 years, with DBP being more important at ages to 50 years, and SBP significant in models of AP thereafter. BMI was significant in multivariate analysis at most ages to 60 years, and DM only at age 50. A detailed examination of the subjects with DM prevalent at age 50, showed six men who developed AP shortly after that age. This small number of subjects precludes meaningful interpretation. Smoking was significantly associated with AP diagnosis only in young men, to age 45 years.

An early case-control study (Stejfa 1967) compared factors in subjects with AP to a control group of the same age, without CHD and free of "hypercholesterinemia". It was reported that those with AP were more likely to have a family history of CHD, hypercholesterolemia and hypertension. Smoking and overweight were not different between cases and controls. A cross sectional Swedish study of 5735 men (Hagman et al. 1987) showed uncomplicated AP in 166 to be associated with SBP, DBP, increased relative body weight, smoking, DM as well as increased serum cholesterol, low leisure time physical activity and stress. During a four year follow up of the Swedish cohort, 128 new cases of AP were shown to be related to DM and increased body weight, but not blood pressure or smoking. In the Framingham report of various manifestations of cardiovascular disease in subjects 35-64 years of age, SBP and body weight, but not DM nor smoking, were associated with AP (Stokes et al. 1987).

In multivariate analysis, it was found that DBP rather than SBP, prior to age 50 years, was more important for the prediction of MI in the MFUS cohort. DM was

significant in the stepwise Cox models at age 50 as was smoking up to age 50 years for models of MI. BMI was important both at younger ages and at ages 55 and 60 years for subsequent MI. The Framingham report (Stokes et al. 1987) found SBP and smoking, but not DM or body weight to be associated with MI occurring before age 65 years. The Goettingen study of MI in 5,790 men age 40 through 59 years reported age, SBP, smoking and plasma glucose in addition to cholesterol measurements to be predictive of MI over a 10 year follow-up period (Cremer et al. 1997). They report a combined incidence of MI and SD to be 5.3 per 1000 pyrs in 10 years through this age group. In their study, a 33 mm Hg change in SBP was estimated to have an odds ratio of 2.0; this corresponds to an odds ratio of 1.23 for a 10 mm Hg change, similar to that for MI reported in this analysis. They estimated a relative risk of MI to be 2.3 for current smokers versus all others. In the MFUS analysis, smokers at age 40 through 59 years had a relative risk ranging from 1.5 to 2.0 compared to non smokers. Diabetics were 2.8 times more likely to develop MI, similar to the relative risk in our study. The Copenhagen City Heart Study (Nyboe et al. 1989, Jensen et al. 1991) of 5,923 men 40 - 69 years of age followed over an average of 6.5 years, found SBP, and treatment for high blood pressure to be strong risk factors for MI. The relative risk of MI increased with grades of smoking, defined on the basis of amount smoked. Diabetics were at an increased risk 1.8 times that of non-diabetics. BMI was only marginally significant in this study for MI.

In this analysis of factors related to SD in the MFUS, smoking was important up to age 55 years, and SBP was significant in models up to age 65 years and BMI was significant up to age 45 years. In the Framingham study, 69 men without prior evidence of CHD were "victims of sudden death" during the first 26 years of follow-up (Schatzkin et al. 1984). Systolic blood pressure, cholesterol, cigarette smoking, left ventricular hypertrophy and age were associated with sudden death. In younger men, Framingham report (Stokes et al. 1987) smoking to be the most important of these risk factors for SD.

7.3.5 The value of risk factor tracking in models of Ischemic Heart Disease

The evidence suggests that young adult males in the top quintile of the distribution of SBP, DBP or BMI are likely to remain in the top quintile at older ages. Tracking was greatest for BMI and more apparent with SBP than with DBP at comparable ages. This evidence raises a question concerning the risk of cardiovascular events in later life associated with high levels of blood pressure and BMI in earlier life. It may be possible that men who "track" in the top end of these distributions from younger adult ages are those who are at greatest risk for cardiovascular disease. This question was investigated in this thesis, and it was found that the MFUS subjects whose blood pressure tracked at higher levels, were in fact at greater risk of subsequent IHD. Similar results were found for those with consistently high BMI.

One objective of this thesis was to identify individual patterns of risk factors that would evolve over time and to model characteristics of these patterns as possible additional factors that might explain variation in risk of IHD for individuals. The

repeated examinations of MFUS subjects over time has resulted in a longitudinal file of routine measurements for each man at advancing ages prior to detection of disease. The number of measurements for each subject is variable and the spacing of examinations is not exact. The distributions of blood pressure and BMI were shown to change with age, both in terms of mean level and variability.

An approach adopted in this thesis to characterise elements of tracking at the level of the individual was suggested by Lauer (Lauer and Clarke 1988). His method was originally applied to longitudinal patterns of blood pressure in children, and has not been applied to prospective studies of IHD in adults. To apply this method, it was necessary to calculate the age-specific percentile of each SBP, DBP and BMI measurement, for each subject, at all ages under observation. For each subject, the ordinary least squares line of the regression of percentile value on age was determined for each risk factor. Three lines for each risk factor and each subject were determined, based on the measurements from entry and prior to IHD up to age 50, 60 and 70 years. Recognising that the distribution of the risk factors change with age, it is important to express this trend over time as a function of the percentile distribution, rather than the actual value of the risk factor, if the descriptors of this line: the slope and variability, are to characterise tracking. These descriptors of an individual's past risk factor profile were considered as independent variables in Cox proportional hazard models, in addition to the variables measured one point in time. This approach proved useful in identifying aspects of SBP, DBP and BMI tracking that improve predictive models of IHD.

The classification of categories of level, trend and variability into discrete groups defined individuals with varying propensities to track. For example, those maintaining a flat trend with age, either at the high, middle or low level of the percentile distribution, would define individuals with a high degree of tracking. For each risk factor, the categorisations of tracking were defined based on all three parameters of the regression equation. These categories provided additional significant information at some ages for models of some endpoints.

In addition to the risk factors measured and included models at age 50, 60 and 70 years, the average percentile level of SBP, DBP and BMI were significant independent predictors for IHD. Level was also significant at age 50 years in models for each of the three IHD manifestations. Categories of BMI tracking added significantly to models at age 50, for IHD as well as endpoints of MI and SD. This is supporting evidence for the value of recognizing higher values of blood pressure or BMI at younger ages, remaining high to early adult life, even if below traditional hypertensive or obese levels, as being important contributors in the identification of high risk young men.

There are few publications in the medical literature examining risk factor tracking in adults as an additional contributor to models of IHD. While methodological approaches vary, the results of the MFUS analysis are similar to those reported in the medical literature. The contribution of variables describing patterns of repeat measurements significantly contribute to models of IHD.

The contribution of repeat SBP measurements to Cox proportional hazard models of IHD were analysed in 1,254 Framingham subjects who survived to age 65 years, free of IHD and antihypertensive treatment (Harris et al. 1985). In that report, the average of SBP measurements before age 65 years was significant ($p<0.05$) while the slope of the regression line of SBP on age before age 65 years and lability of SBP defined by the standard deviation of previous SBP measurements contributed marginally to models of IHD incidence. The Honolulu Heart Study reported that with four measurements of SBP between ages 40 and 50 years, that the variability about the regression line, but not the slope of the regression of SBP on age itself were significantly associated with an increased risk of incident definite CHD over a 11.6 year follow-up period (Grove et al. 1997). The Honolulu Heart Study also reported that the variance of BMI measurements over the 10-year period to contributed significantly to the Cox models of incidence IHD.

7.4 Effect modification of risk factors for Ischemic Heart Disease

7.4.1 Statistical considerations

When interpreting the relative risk representing the association between a risk factor and disease onset over a period of time, a distinction must be kept between two analytic situations defined by time of measurement of risk factors. The value of a risk factor can be fixed in time, measured once at baseline, and its effect modeled on development of disease over time since baseline. Alternatively, the value of a risk factor

can be measured repeatedly and updated values over time incorporated into a time dependent covariate model of disease.

Risk factors were measured at one point in time and their effects on risk quantified over varying follow-up time both in the Honolulu Heart Study (Benfante et al. 1989) as well as in the Framingham report (Kannel and Larson 1993) discussed above. Both these reports interpreted risk factors in light of their effect for early onset or later onset disease. In the MFUS analysis, age-specific models of risk factors for subsequent IHD were examined using models at the 5-year age examinations. The varying effect over time of each risk factor at these ages was examined by testing the proportional hazard assumption of the Cox model. For the risk factors measured at a specific age, an interaction term with the risk factor and time under study since that examination was modeled. A significant interaction term in the model would indicate that the risk factor, measured at one point in time, had a different effect, i.e. a varying relative risk, that depended on the length of time since examination. There was evidence in the MFUS analysis with the smoking variable at younger ages to have a changing effect over time. Subjects changed smoking classification during the course of the study, for example, smokers at younger ages may have quit smoking during follow-up, and hence lowered their risk of IHD at later follow-up times.

A risk factor may be updated over time on repeat measurement at different ages, and the effect of the risk factor may be changing depending on the age at examination. This consideration was examined by modeling each risk factor as a time dependent

covariate by updating values of covariates based on the measurement determined at the 5-year interval examinations prior to IHD. The significance of an interaction term defined by the product of the current value of the risk factor and age at examination tested whether the effect of a level of the risk factor depended on the age at the examination when it was measured.

Another statistical consideration concerns effect modification. When interpreting effects modified by another variable, a distinction must be made between risk ratio (or incidence ratio) and risk difference (or incidence difference) measures arising from multiplicative and additive models, respectively (Rothman 1986). As an example of this, a comparison of the effects for smoking, hypertension and high blood cholesterol as modified by age were examined for CHD incidence and stroke in men and women over 30 years of follow-up in the Framingham cohort across 10-year age categories from 35-44 years through 75-84 years (Psaty et al. 1990). For both smoking and increased serum cholesterol, the risk ratio for CHD incidence decreased with age, while the risk difference did not change. The risk ratio for hypertension and CHD incidence did not significantly change with age but there was marginal evidence for a significant increase in risk difference. Hence, effect modification may be present, but the effect must be interpreted in light of an additive (risk difference) or multiplicative (risk ratio) model.

Effect modification by age on risk factors for IHD in the MFUS data was explored graphically by examining the incidence of IHD across quintiles of SBP, DBP and BMI, and in categories for DM and smoking. The ID and IR for this representation of the data

were calculated for the data, and trends in the ID and IR described over age. Similar to the IR, the relative risk for IHD was calculated for a fixed difference in SBP, DBP and BMI using the Cox model. While no obvious trend in IR with age was apparent, significance evidence for a decreasing relative risk with age was found. This seeming inconsistency can be explained by recognising that the relative risk from the Cox model relates a unit difference in SBP (or a 10 mm Hg difference in SBP) to risk of IHD, while the IR is the ratio of the incidence of IHD in the top quintile to the bottom quintile, and with increasing age, represents subjects with a minimum difference in SBP for example, of 18 mm Hg at age 40 years, 21 mm Hg at age 50 years, 30 mm Hg at age 60 years and 33 mm Hg at age 70 years. Hence, with increasing age, the effect being contrasted with the trend in IR, is the effect of an increasing difference of SBP.

7.4.2 Interpretation of the changing effect of risk factors for Ischemic Heart Disease

It would be incorrect to interpret the declining relative risk of IHD with age for blood pressure and smoking to mean that these risk factors are not important at older ages. There has been caution expressed with regard to the interpretation of aging effects on risk factors in recent review articles (Kaplan et al. 1992, Kaplan et al. 1999) and specifically for effects on IHD in the MFUS cohort (Tate et al. 1998) in an accompanying editorial (Howard and Goff 1998). In the examination of risk factors in the elderly (Kaplan et al. 1992) it was suggested that reasons for the declining trend of relative risk include selective mortality or "survivor effect", a lack of tracking of risk factors, change

in the physiological impact of risk factors and change in the clinical manifestation of disease. These reasons will be described in the forthcoming paragraphs.

One possible explanation is that subjects with and without a particular risk factor are viewed to be composed of two subgroups, one group susceptible to disease and one group not susceptible to disease. The survivor effect describes a situation where subjects susceptible to IHD and having the risk factor (either higher blood pressure or smokers for example) develop IHD at a greater rate than the group of susceptible subjects without the risk factor. So with advancing age the group of susceptible subjects with the risk factor is diminishing at a greater rate than the group of subjects without the risk factor. Hence, with advancing time, and age, the two groups are becoming more alike in terms of their rate of disease, and hence the relative risk associated with the risk factor is diminishing.

The relative risk associated with a risk factor for IHD may be declining because risk factors at younger ages may be more strongly correlated than risk factors at older ages. This may bias results towards no association of risk factors and IHD at older ages. The premise is that there is a strong positive correlation between IHD risk factors at younger ages, and therefore at least part of the greater effect that is reflected through larger risk ratios for blood pressure and smoking at younger ages, could be due to a greater likelihood of clustering of risk factors. Those who develop IHD earliest in a cohort study, would be more likely those who have multiple risk factors. Therefore, those remaining at risk of IHD to older ages will have less clustering of their risk factors and hence there will be fewer high risk individuals with multiple risk factors. The

changing correlation structure of risk factors with age has not been examined in the MFUS as a possible reason for the declining effect of risk factors.

There may be a greater chance of misclassification of disease state in the elderly in contrast to the younger men. This could arise because of the prevalence of subclinical CVD. The argument is, that in the young there is a lower prevalence of atherosclerosis, and hence a lower likelihood of misclassifying a subject without IHD as having IHD. In the elderly, atherosclerosis is more prevalent, and with the higher prevalence of atherosclerosis comes a greater chance of misclassifying a subject without IHD as having IHD. These misclassifications would tend to dilute the strength of the association of these risk factors with IHD. In MFUS, diagnosis of IHD was made prospectively with previous electrocardiograms and clinical records for reference. The likelihood of misclassification of IHD should be considered lower than what might be expected in the general population.

Further, a caution was expressed that reduced relative importance with age should not be interpreted that the risk factor is less important. From a public health perspective, in terms of the burden of disease in the population, recognition that the incidence of IHD continues to increase with age, and hence is much greater at older ages than at younger ages, translates into a greater absolute effect, risk difference, for blood pressure and smoking, even though the relative effect for each of these two factors is reduced.

Even though the incidence density of IHD continues to increase after age 65 years, the risk factors examined after this age in the MFUS, except for blood pressure and

MI, appear to be unassociated with new IHD events. It is not likely that this could be attributed to differential survival of MFUS cohort members, as a high internal validity was maintained through the small number of subjects lost to follow-up and a high rate of completion of follow-up examinations. Further, differential survival arising from early deaths of smokers does not seem likely, as the proportion of never smokers remained relatively stable from younger to older ages. Other studies have concluded that the risk factors examined here, as well as serum cholesterol, appear to be poor predictors of late onset coronary heart disease (Rose and Marmot 1986, Seltzer 1975).

7.5 Conclusions and implications of findings

IHD is an important health problem in our society and continues to be a major cause of morbidity and mortality in the elderly. Consequently, the identification of factors associated with IHD and quantification of levels of risk should be of ongoing interest for the primary prevention of this disease.

In MFUS, based on multivariate modeling of risk factors, the young man at greatest risk of IHD is the overweight smoker with elevated blood pressure. By middle age, DM is an additional important factor, while the effects of smoking and blood pressure measured at that time, although still significant, are diminished. The tracking of both blood pressure and BMI to age 50 years, provided additional independent information to these models. By age 60 or 70 years of age, when current values of blood pressure were of less importance, and BMI was not statistically significant, patterns

established by previous blood pressure and BMI measurements contributed significantly to models of IHD. The relative risk of IHD associated with each risk factor changed very little from univariate to multivariate analysis, providing supporting evidence for the independence of the effects of each of these risk factors.

It is evident that the profile of significant risk factors for IHD changes with age. The magnitude of effect and relative importance of risk factors for IHD is also changing. This dynamic relationship must be kept in mind when planning strategies for prevention of cardiovascular disease. The patterns of risk factors evolving from repeated measurement over time in the young men of the MFUS cohort, specifically characterisation of the relationship between blood pressure or BMI with age, should be included as an important considerations in the planning of primary preventive strategies for IHD.

While it is recognized that incidence of IHD increases across all levels of blood pressure, the results of this thesis provide supportive evidence that high blood pressure levels, and hence increased risk of IHD, are identifiable from young adult ages. Further, the tracking characteristics of blood pressure at repeat measurement over time, exhibited by young men, at levels below hypertensive values, significantly contribute to predictive models of IHD, beyond the contribution to models of current values.

The dissemination of these findings to the medical community will increase awareness of these issues. Reduction of incident IHD could result if blood pressure could be moderated before hypertensive levels are reached and prior to ages at increasing

incidence of IHD. As Dr William Kannel of the Framingham Heart Study stated in his address at the 1997 Canadian Cardiovascular Society annual meeting, "The day must come when a first coronary event is not a signal for treatment, but rather a sign of medical failure."

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9 APPENDICES

9.1 Appendix 1: Letter from the Faculty Committee on the Use of Human Subjects in research, University of Manitoba. October 10, 1996

THE UNIVERSITY OF MANITOBA

FACULTY OF MEDICINE
Human Ethics Office

Human Ethics Committee
A111 - 753 McDermot Avenue
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Tel: (204) 789-3255
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October 10, 1996

Dr. T. E. Cuddy
Section of Cardiology
Health Sciences Centre

Dear Dr. Cuddy:

RE: Manitoba Follow-Up Study

With respect to the Manitoba Follow-up Study, the Committee is well aware this study is continuous since the late 1940's, that data is kept strictly confidential and subjects have given consent and are well informed.

This meets all the requirements of the Faculty Committee on the Use of Human Subjects in Research.

Yours sincerely,

THE UNIVERSITY OF MANITOBA

Gordon R. Grahame, M.D.
Faculty Committee on the Use of
Human Subjects in Research.

GRG/ll

9.2 Appendix 2: Peer reviewed publications from the Manitoba Follow-up Study

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17. Rabkin SW, Mathewson FAL, Tate RB. The Relation of Blood Pressure to Stroke Prognosis. Ann Int Med 1978;89:15-20.

18. Rabkin SW, Mathewson FAL, Tate RB. Long Term Changes in Blood Pressure and Risk of Cerebrovascular Disease. Stroke 1978;9(4):319-327.

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20. Rabkin SW Mathewson FAL, Tate RB. Longitudinal Blood Pressure Measurements During a 26 Year Observation Period and the Risk of Ischemic Heart Disease. Am J Epidemiol 1979;109(6):650-662.

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