USE AND EVALUATION OF A REGISTER FOR A WELL POPULATION IN STUDIES ON CARDIOVASCULAR DISEASE AND DIABETES IN THE WEST OF SCOTLAND

BY

© MOHSEN JANGHORBANI M.Sc.

THESIS SUBMITTED IN PARTIAL SATISFACTION OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

TO

THE DEPARTMENT OF COMMUNITY MEDICINE

FACULTY OF MEDICINE

UNIVERSITY OF GLASGOW

VOLUME 1

DEDICATION

I dedicate this work to the memory of my late brother, Dr. Mojtaba Janghorbani, who died during this study and whom I miss.

CONTENTS **PAGE**

VOLUME ONE

CONTENTS

CONTENTS

CONTENTS

CONTENTS

CONTENTS

CONTENTS

CONTENTS

VOLUME TWO

LIST OF MAPS, FIGURES AND TABLES

CHAPTER 1

CHAPTER 4

CHAPTER 5

CONTENTS

CONTENTS

CONTENTS

CONTENTS

CONTENTS

ACKNOWLEDGEMENTS

Many people have helped me with various aspects of this project. I would like to thank everyone who provided guidance, knowledge and friendship. In addition, there are several persons I would like to acknowledge individually.

Firstly, I am extremely grateful to Professor A.J. Hedley, my thesis chairman. He has provided intellectual guidance, advice and encouragement since I commenced my research project.

Special thanks go to Dr. R.B. Jones for his generous advice and inspiring example, in areas both intellectual as well as personal.

Also deserving my appreciation is Mr. W.H. Gilmour for his help in implementing and understanding the statistical techniques used in my work.

I would also like to thank Mr. K.J. Murray for guiding and instructing me in the complex field of computer science.

I am indebted to Dr. C.R. Gillis and Mr. D. Hole for making available to me the data from the Renfrew and Paisley study. Dr. C.R. Gillis was one of the original members of Midspan team and I would like to thank him particularly for his invaluable advice and help. Mr. D. Hole's knowledge of the data and his intellectual insight were extremely helpful in the initial stages of my project.

My thanks are also due to Dr. A.P. Curran, Dr. R.P. Knill-Jones and other member of the Community Medicine

Department staff for their continuous encouragement.

I am most grateful to the residents of Renfrew and Paisley who participated actively in this project and to the Argyll and Clyde Health Board Area general practitioners for their cooperation with surveys and follow-up of patients.

I am indebted to Mr. W. McMaster and his staff of the Scottish National Health Service Registry of the Registrar General for collection of the mortality data and medical record linkage of mortality and to the Argyll and Clyde Health Board for permission to link the Renfrew and Paisley file with the community health index.

I am especially grateful to Professor V.M. Hawthorne for his permission to use the Renfrew and Paisley data for the purpose of this study; he designed, set up and directed the Midspan project from its inception and without his foresight and initiative this project would not have been possible.

Finally, I would like to thank my parents for their encouragement throughout my educational career, and especially my wife, Motahareh, for her unending support, patience and care of our son, Mehran, and for her tolerance of my frequent absences from home during the completion of this thesis which would have been much more difficult without her encouragement, support and tolerance.

LAYOUT OF THE THESIS

Volume 1 of the thesis contains the text for the 14 chapters. All figures, tables , maps, references and appendices are presented in a separate volume so that the reader can refer to them while reading the text without having continually to turn back pages. Each chapter has a coloured first page for easy access, with a summary and contents. Each chapter from chapter 6 to 13 has a separate introduction, results and discussion for easy follow-up, and a general discussion of the entire thesis is presented in chapter 14. Figures, maps and tables are numbered sequentially for each chapter; for example, in chapter 5 thare are tables 5.1 to 5.13. References are numbered sequentially throughout the thesis. The second volume also contains appendices of questionnaires used for baseline data collection, a follow-up and coding schedule and a list of Midspan publications since 1964. Appendix D of the second volume contains a separate paper concerning national mortality trends, with emphasis on mortality trends from stroke, since 1950.

ABSTRACT

Cardio-respiratory diseases and cancer are the most important causes of mortality and morbidity in west central Scotland. From 1972 to 1976, more than 16,000 men and women were recruited to a well-population study (Renfrew and Paisley as part of Midspan) of cardio-respiratory diseases and risk factors including 10,541 men and women aged 45-64 whose baseline casual blood glucose was measured. This population was "flagged" with the National Health Service Central Registry (NHSCR) and has been followed up for mortality. By 1986, sufficient deaths had occurred to allow an opportunity for epidemiological research. This study therefore 1) examined the quality of data available from the Midspan survey, 2) explored its use in answering a number of epidemiological questions, and 3) evaluated the potential for further follow-up studies.

1.The establishment and performance of the Midspan register for a longitudinal study has been evaluated. The initial survey had a response rate of about 80% but a major limitation of these data is that 30% of blood glucose values were not measured and there also appears to be a nine percent shortfall in various stages of the reporting of mortality events.

2.Variation in mortality risk has been examined while adjusting for seven crdiovascular disease (CVD) risk factors measured on recruitment (gender, systolic blood pressure (SBP), diastolic blood pressure (DBP) serum cholesterol, blood glucose, body mass index (BMI), and

smoking) in a series of age-adjusted and multiple logistic regression (MLR) analyses.

The main aim has been to re-test the hypothesis that high casual blood glucose is a risk factor for CVD, ischaemic heart disease (IHD), stroke and all causes mortality. Univariate analysis showed that, excluding known diabetics, individuals with blood glucose above the 95th centile have a higher mortality rate than those in the lowest 5 percent. Multivariate analysis showed that initial casual blood glucose level is a significant risk factor for subsequent mortality. Age, blood pressure, cigarette smoking and gender were also significant predictors.

Most previously published studies of asymptomatic hyperglycaemia had only included males so it was decided that gender differences should be analysed in more detail by carrying out MLR analysis for males and females separately. High blood glucose level was a risk factor for CVD mortality in both genders. It was also a risk factor for all causes, IHD and stroke mortality in women but not in men. Asymptomatic hyperglycaemia therefore shows to a lesser extent the same gender differentials in risk of mortality as have been demonstrated by studies carried out elsewhere amongst known diabetics. On the other hand, repeating the original MLR analysis and allowing for interaction between gender and the other cardiovascular risk factors showed that the seven cardiovascular risk factors considered do not account for the overall gender difference in mortality rates.

Some other studies had suggested that blood glucose

level was associated with other CVD risk factors, particularly with BMI, so it was decided to investigate the extent to which the blood glucose level interacts with BMI in the prediction of all causes and CVD mortality. Associations between BMI and all causes deaths were U shaped. There was no relationship between BMI and CVD deaths, neither for normoglycaemics nor hyperglycaemics. The MLR analyses showed that BMI was not a predictor of cardiovascular deaths or of IHD deaths independently of the other risk factors. BMI was slightly negatively associated with overall causes of death and stroke deaths. This relationship depended on smoking as an interaction term for overall causes, and gender and age for cerebrovascular disease deaths.

Lastly, as there was conflicting evidence in the literature, the relative importance of SBP compared to DBP and other combinations of SBP and DBP in predicting the risk of IHD and stroke mortality was re-examined. MLR analysis was used to assess the comparative strength of SBP, DBP, mean arterial pressure (MAP), mean arterial index (MAI) and pulse pressure (PP), for the prediction of IHD and stroke mortality after adjustment for the other CVD risk factors for both males and females. While all measures of blood pressure were associated with IHD and stroke mortality, the risk of IHD deaths was more strongly associated with MAI and SBP alone in both males and females. SBP and DBP together, MAP and PP do not predict future IHD mortality better than SBP alone or MAI.

SBP and DBP are strongly correlated in both genders

(r=0.66, P<0.001) but their relationship with stroke mortality was different between males and females. In females the risk of stroke mortality was more strongly associated with DBP; in males SBP and DBP have the same predictive strength of stroke death. These findings suggest that the predictive strength of SBP and DBP for stroke mortality may depend on age and gender.

3.The feasibility of following up a cohort through record linkage using the Midspan registry, community health index (CHI) and general practitioner (GP) records has been assessed. Identification details of the Midspan file were used to identify patients on the CHI. 937 (96%) out of 981 were identified and were asked to complete a questionnaire about their current diabetes status. Follow-up response to three sets of mailings totalled 80%. By contacting the GPs of non-respondents complete data was obtained for 903 (96%) people showing the feasibility of such follow-up studies. The cohort consists of 224 people in the top 5% of casual blood glucose distribution (>126 mg/dl), 426 in the lowest 5% (<70 mg/dl), and 253 in the middle 5% (=90 mg/dl), all of whom did not have a diagnosis of diabetes mellitus at the time of the initial survey in 1974-76. Life-table analysis was used to estimate a 12-14 year incidence of overt diabetes. This was 9 times higher in men and 15 times higher in women for those in the top 5% compared to the other two groups. The risk of diabetes in overweight persons was significantly higher when blood sugar was above 126 mg/dl. This study has shown that despite some limitations in the data, the Midspan file has a unique potential to contribute to the

epidemiology of cardio-respiratory disease with respect to both mortality and morbidity.

PAPERS IN PREPARATION: available in manuscript form.

The work described in this thesis is in a stage of advanced preparation for publication, as follow:

1. An epidemiological investigation of interaction between asymptomatic hyperglycaemia and body mass index in the prediction of cardiovascular mortality risk.
2. Fourteen year prospective population based study of association between asymptomatic hyperglycaemia and risk of cardiovascular and all causes mortality in a middle-aged population in two Scottish town.
3. A prospective population based study of gender differential in mortality from cardiovascular disease and all causes in asymptomatic hyperglycaemics.
4. An epidemiological assessment of the components of blood pressure as predictors of ischaemic heart disease mortality in a middle-aged population in the west of Scotland.
5. Systolic and diastolic components of blood pressure as predictors of stroke mortality in a middle-aged population in the west of Scotland.
6. A prospective population based study of gender differential in mortality from cardiovascular disease and all causes.
7. Trends in mortality from stroke in Scotland, 1950 to 1986.
8. Community health index and general practitioner record linkage for cohort follow-up purposes.
9. Cohort follow-up using record linkage to measure the

association between high casual blood glucose value and later development of overt diabetes in west of Scotland.

THE CHAPTERS

Chapter 1 outlines the Midspan Project, the data archive, its use and potential for further cardiovascular study, and reviews similar cohorts and population studies.

Chapter 2 reviews the literature and discussion of problems encountered in (a) determining associations between mortality and asymptomatic hyperglycaemia; (b) gender differentials in mortality from an epidemiological point of view and (c) the comparative importance of SBP and DBP in predicting IHD and stroke.

Chapter 3 outlines the study design to be used to test the operational hypotheses that:

any positive association between hyperglycaemia and cardiovascular disease mortality is independent of other cardiovascular risk factors;

there is no interaction between hyperglycaemia and BMI in prediction of all causes, CVD, IHD and stroke mortality;

SBP is a better predictor of IHD and stroke mortality than DBP or different combinations of SBP and DBP.

Chapter 4 describes the population and methods, including sample size, data collection method, definition of the study population and statistical procedures used during the course of study.

Chapter 5 describes the baseline situation, mortality pattern and mortality linkage used in Midspan.

Chapters 6 to 11 present the results and discussion of the different studies both descriptive and analytical.

Chapter 6 contains results and discussion concerning the relationship of hyperglycaemia to cardiovascular mortality risk and interaction effects of blood glucose levels, with other cardiovascular disease risk factors.

Chapter 7 gives the results and discussion regarding gender differentials in mortality from cardiovascular and all causes in asymptomatic hyperglycaemics.

Chapter 8 contains results and discussion relating to the interaction between asymptomatic hyperglycaemia and BMI in the prediction of cardiovascular and overall mortality.

Chapter 9 presents the results and discussion relating to gender differentials in mortality from CVD, and all causes, in the cohort population under study.

Chapters 10 and 11 gives the results and discussion regarding an epidemiological assessment of SBP and DBP and derived combinations of them as predictors of IHD and stroke mortality.

Chapter 12 reviews the concept of medical record linkage and contains results and discussion regarding the feasibility of the follow-up of a cohort, through record linkage using the Midspan registry, CHI, and GP records.

Chapter 13 serves as an example of the feasibility of the long-term follow-up of a cohort using record linkage and contains results and discussion pertaining to the predictive value of a casual blood glucose measurement for subsequent progress to clinical diabetes. It also discusses whether in subjects with high blood glucose other characteristics such as BMI, gender, smoking, blood pressure and serum cholesterol are associated with the

risk of deterioration to diabetes.

Chapter 14 includes a final general discussion and conclusions regarding the feasibility and practical difficulties of this study, risk factors, methodology, and unanswered questions together with recommendations for future studies.

LIST OF ABBREVIATIONS

ABI	Atherothrombotic Brain Infarction
AMI	Acute Myocardial Infarction
BMDP	Biomedical Data Processing
BMI	Body Mass Index
CHI	Community Health Index
CI	Confidence Interval
cm	Centimeter
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
DBP	Diastolic Blood Pressure
EEG	Electrocardiography
F	Female
GP	General Practitioner
GRO	General Registrar Office
GTT	Glucose Tolerance Test
hr	Hour
IHD	Ischaemic Heart Disease
ICD	International Classifications of Diseases
ICL	International Computer Limited
ISD	Information Service Division
Kg	Kilogram
M	Male
m	Metre
MAI	Mean Arterial Index
MAP	Mean Arterial Pressure
mg/dl	Milligram Per Deciliter
MLR	Multiple Logistic Regression
mm	Millimetre

LIST OF ABREVIATION

mmHg	Millimeter of Mercury
mm/sec	Millimetre per Second
MMR	Mass Miniature Radiography
MRC	Medical Research Council
NHS	National Health Service
NHSCR	National Health Service Central Registry
NS	Not Significant
OD	Odds Ratio
PLR	Programme Stepwise Logistic Regression
PP	Pulse Pressure
PYO	Person Year of Observation
RR	Relative Risk
SBP	Systolic Blood Pressure
SD	Standard Deviation
SHIPS	Scottish Hospital In-Patient Statistics
SND	Standard Normal Deviate
SOR	Standardized Odds Ratio
SPSS	Statistical Package for the Social Sciences
USPHS	U.S. Public Health Service
WHO	World Health Organization
Yr	Year

CHAPTER 1

GENERAL BACKGROUND OF MIDSPAN PROJECT

SUMMARY: The Midspan Health Project is an epidemiological screening survey of about 30,000 men and women identified by occupational group or by census of the general population in the west of Scotland and directed toward the study of IHD, stroke, bronchitis, cancer and tuberculosis. The Renfrew and Paisley study is a part of the Midspan project consisting of a well middle-aged population based study. Long-term follow-up of the Renfrew and Paisley population has been achieved by continuous medical record linkage through the NHSCR for mortality and for ad-hoc studies with the Scottish Hospital In-patient's statistics (SHIPS) for morbidity. Record linkage with the West of Scotland Cancer Registration Bureau and the local chest clinic has been set up to produce data related to the development of cancer and tuberculosis and other diseases of the chest. Although since late 1950 and early 1970, a number of large cohort studies of occupational and general populations were being recruited in many parts of the world, to study the role of risk factors in the aetiology of CVD, Midspan is undoubtedly a unique resource containing the only well general population survey carried out in the United Kingdom.

Contents

CHAPTER 1

1.1. INTRODUCTION

Between 1972 and 1976 the Department of Community Medicine, University of Glasgow undertook to study the factors associated with the development of cardio-respiratory disease and cancer and to determine the incidence and prevalence of tuberculosis by the long-term surveillance of a sample of the middle-aged population of Renfrew and Paisley, in west central Scotland. The study has been reported in various stages by Professor VM Hawthorne and others; key findings have been presented in various papers which are included in appendix C. However, it is useful to reconsider at this time the reasons for bringing the study into being and to prepare a systematic account of the major findings and to review similar studies. This chapter reviews this past experience as a prelude to the new programme of evaluation and original epidemiological studies.

Credit must be given to those people who have worked on the Midspan project over the years. But, of course, special credit must go to Professor VM Hawthorne as director of the study, and Dr. CR Gillis as co-director of the project, and Mr. D Hole and Mr. WH Gilmour as statisticians who brought together from the beginning a unique combination of medical and statistical competence. It is their contributions over many years that make this study possible.

1.2. REVIEW OF SIMILAR COHORT STUDIES

A major goal of epidemiologic research is to identify factors involved in the aetiology of diseases to prevent

or control such diseases. Arteriosclerotic CVD, particularly IHD and stroke, leads to more deaths, disability, and economic loss than any other diseases in many industrialized societies since 1950. Recently, a tremendous amount of research has been devoted to examine the possible causes and pathogenesis of CVD. These researches have focused primarily on basic biological mechanisms and on improvements in medical care, but considerable research also has been done on the epidemiology of CVD and it is to that body of evidence that this section is directed.

In the late 1940s, the great public health impact of CVD was beginning to be appreciated, but little was known about factors which put one at increased risk of the disease. However, for a meaningfull policy to be developed, it was imperative that these factors be systematically studied and evaluated. For the first time, the U.S. Public Health Service began to lay plans for a longitudinal study of CVD to follow a large population of people for many years. This study, initiated in Framingham, Massachusetts, was soon followed by several other large cohort studies of occupational and general populations in America, Europe and other parts of the world primarily to investigate the role of risk factors in the aetiology of CVD. In USA, results from Framingham, Albany, Chicago, Los Angeles, Minnesota, and Tecumseh studies eventually combined into the so-called Pooling Project. In England, the Whitehall study of male civil servant started in the late sixties and in Scotland the

Midspan study, involving both occupational and general populations was initiated in the mid sixties. In the U.K., Midspan is undoubtedly a unique resource containing the only general well-population survey carried out. In this section I have attempted to review briefly the important epidemiological studies of CVD before describing the Midspan study in detail.

The Whitehall Study (1) is a screening survey for cardiorespiratory disease and diabetes among 18,403 non-industrial male civil servants aged 40-64 years in 1968-70, representing a 77% response of those eligible. The department of medical statistics and epidemiology, London School of Hygiene and Tropical Medicine, undertook clinical measurements and carried out the trial of smoking prevention measures. The department of medicine, Guy's Hospital Medical School, had responsibility for the biochemical aspects of screening and for the trial of therapy in those with raised blood sugar.

The Busselton Survey (2) is a study of a total rural community in Western Australia. In 1966, based on a census of residents from recent electoral rolls, invitations were sent to 3,719 adults aged 21 and over in the defined population asking for their participation in a screening survey aimed at a description of disease prevalence and at early detection of chronic disease, particularly of cardiovascular disease. Screening was conducted in a concentrated period of 2 weeks, and 3,410 adults attended (91% response rate), with complete records obtained for 3,331.

The Glostrup Population Studies (3) are extensive

health surveys of a total population aged exactly 40, 50, 60, 70, and 80 years old. When the study of 50 year olds was initiated in 1964 the main purpose was an investigation of risk factors for IHD in men and women. The seven municipalities chosen for the investigation are in the western suburbs of Copenhagen. The region has experienced the change in Danish society from agriculture to industry. In 1964 the area was fairly representative of the total Danish population at that time in terms of occupation and distribution of other major socio-economic characteristics. In 1964, the area included 514 men and 461 women born in 1914. The response rate was 85% of those eligible.

The Helsinki Policemen Study (4) is a prospective study on IHD and other atherosclerotic vascular disease and their risk factors. During the period from March 1966 to February 1967, a total of 1,326 men aged 30 or over participated in the initial examination of the Helsinki Policemen Study. The response rate in this study was 98.4%.

A comprehensive community programme for control of CVD was carried out from 1972-1977 in the county of North Karelia, Eastern Finland, an area with exceptionally high CVD rates (5). The project was started in response to a petition from the local population requesting that something be done about the cardiovascular problem. The main objective was to reduce the mortality and morbidity of CVD among the population, particularly in middle-aged men. The intermediate objectives were a general reduction

of smoking, serum cholesterol levels and elevated blood pressure among the whole population; early detection, treatment and rehabilitation of CVD patients were also promoted in the area. More than 10,000 subjects were studied each time, with a participation rate of around 90%.

The Social Insurance Institution's Coronary Heart Disease Study (6) is a prospective population study designed to investigate the prevalence, risk factors, incidence and prognosis of IHD in middle aged Finnish men and women. The study population contained 12 population groups drawn from four regions of Finland, a total of 5,738 men and 5,224 women aged 30-59 year. The study started in 1966 and the basic examination was completed in 1972. The overall response rate to the investigation was 83%. Nine of the groups consisted of all or a random sample of the population from a defined geographical area. Four of these areas were urban or semiurban and five rural. The other three study cohorts consisted of all employees of a factory (two paper mills, one steel factory).

The Paris Prospective Study (7) was designed in 1965 in order to give some insight into the frequency of clinical complications of atherosclerosis (cardiac and non-cardiac) in a total occupational based French population and to evaluate their risk factors. Between 1967 and 1972, 7,990 men aged 42-53 working in the Paris Civil Service entered the study, they were invited to receive an annual cardiovascular screening examination (history, ECG, biological tests and clinical examination).

The Basle Longitudinal Study (8), conducted by the Division of Angiology, Department of Internal Medicine, University of Basle, was initiated in 1959, when 6,470 of the total of approximately 22,000 persons employed by the local pharmaceutical industry were examined. Basle is a city of some 250,000 inhabitants and is situated in the north-west corner of Switzerland where the frontiers of France, Germany and Switzerland meet. The second study followed in 1965-68. A third study began in 1971 and was conducted in 1973. The Basle Longitudinal Study had a variety of aims. The primary objective was to establish the prevalence and incidence of peripheral arterial and venous disorders and of IHD in a working population.

The Manitoba Study (9) is the follow-up of a cohort of 3,983 subjects aged 15 and over, who during World War II were either pilots or pilots-in-training in the Royal Canadian Air Force or pilots licenced by the Department of Transport. During World War II all these subjects had a routine electrocardiogram in addition to regular medical examination. After release from the service, a few continued to fly, but the majority found different occupations and are in all strata of society. For each subject, measurements of age, blood pressure, body weight and height at the examination time, 1948, were selected as the entry examination. Earlier medical examination provide evidence that they were without clinical manifestation of IHD or cerebrovascular disease when the population was defined. Since then they have been followed by annual mail contact and periodic examinations at 5 and later 3 yearly

intervals. Annual contact has been lost with only one person.

In 1948 the United States Public Health Service undertook to study the factors associated with the development of atherosclerotic and hypertensive cardiovascular disease by the long-term surveillance of a sample of the adult population of Framingham, Massachussetts (10). A probability sample by household of two thirds of the adult population, aged 30 to 62 years, based on an annual town census for voting purposes maintained by the town, was chosen for study. It was possible to bring in for examination 68.6% of the 6,510 selected. They received cardiovascular examinations biannally where measurements of blood pressure, daily tobacco use, weight, ECG findings and a variety of biochemical tests, including cholesterol and glucose, were obtained.

The Western Collaborative Group Study (11) is a prospective epidemiological study of 3,154 initially well men, aged 39-59 years at intake in 1960-61, who were employed in ten participation companies in California. Data collection was terminated with the annual follow-up examination in 1969, resulting in 8.5 years of follow-up.

During the period from 1967 to 1973 the Chicago Heart Association Project in Industry (12) was started and screened 39,573 individuals employed in 84 companies and organisations in Chicago. The volunteer rate was approximately 55% of the work force employed by these firms. The total number of persons screened for each of the four major gender-race groups were 20,233 white males,

14,368 white females, 1,494 black male and 2,330 black females. Participants were followed prospectively to ascertain vital status.

Between 1972 and 1974, 82% of adult residents of an older, white, upper-middle-class community of Rancho-Bernardo, California, were surveyed for heart disease risk factors (13). This cohort has been followed for vital status for an average of nine years. At the time of the initial visit, participants were interviewed by means of standard questionnaire and given a limited physical examination.

The Pooling project Research Group (14) comprised eight longitudinal investigations on the incidence of IHD in middle aged white men. The major aim of the project was to refine predictive indices for various manifestations of IHD in terms not only of single risk factors, but also risk factors in combination. It was hypothesized that pooling data from several studies would yield analytical results giving increased assurance concerning the relationship of key risk factors to IHD, and more precise quantitative estimates of their importance, both on their own and in combination, than individual studies permitted.

Six studies were originally involved in 1964 in the pooling project -The Albany Cardiovascular Health Centre Study, Chicago Peoples Gas Co. Study, Chicago Western Electric Co. Study, Framingham Heart Disease Epidemiology Study, Los Angeles Heart Study, and Minnesota Business and Professional Men Study. At that time these seemed to be the only major long-term epidemiological investigations of

IHD in United States with extensive follow-up information sufficiently uniform to be pooled. Subsequently the University of Minnesota based Railroad workers study and Tecumseh Health Study were added.

Each study attempted to secure the participation of as large a proportion as possible of its defined population. The proportion were: Albany 87%, Chicago Gas Co. 92%, Chicago Western Electric Co. 67%, Framingham 69%, Los Angeles 75%, Minnesota Business and Professional Men (not applicable), North-West Railroad Workers 66%, Tecumseh almost 90% of the total community population.

Most of these studies were performed in male occupational groups and none of them had a plan to continue follow a cohort of individuals until death.

1.3.HISTORY OF MIDSPAN PROJECT

Tuberculosis has a special and historic place in the studies of cardio-respiratory disease that began in the west of Scotland in the mid-sixties. It was the success of the mass radiography campaign against tuberculosis in Scotland between 1957 and 1959 that suggested the use of a similar screening technique to detect bronchitis, hypertension, angina and other symptoms of coronary ischaemia. Not only did the campaign suggest the method of study, but its detection of 8,000 out of the total of 12,000 new active cases of infectious pulmonary tuberculosis in Glasgow and the west of Scotland clearly indicated the importance of its location. Used as a general index of morbidity in the country, tuberculosis made the City of Glasgow the natural venue for research directed not only toward the eradication of tuberculosis,

but also towards the development of mass health examination for the whole range of chronic cardio-respiratory disease.

Shortly after the end of the 1959 compaign and a series of mopping-up operations which took the Scottish units as far south as Liverpool, routine mass radiography of the chest was supplemented by multiphasic screening procedures in units of the then Western Regional Hospital Board Mass Radiography Service.

The multiphasic cardio-respiratory screening procedure was administered first to occupational groups being visited routinely in the Mass Radiography Service Programme for the control of pulmonary tuberculosis. Then in 1967 the first of three census-identified surveys of the whole general population, was mounted on the Island of Tiree. After a further interval, 7,000 individuals in various occupational groups were examined throughout the west of Scotland. As a result of these studies it was proposed that a major epidemiological study be carried out in the Scottish Burghs of Renfrew and Paisley. The aim of this study was to examine the feasibility of accelerating the decline of tuberculosis and, at the same time, reducing the risk of cardio-respiratory disease and disability. In the event the request was jointly accepted for support by the trustees of the King Edward Memorial Trust and their scientific advisors in 1969. The trust agreed to support the tuberculosis research and the Scottish Home and Health Department the research in cardio-respiratory disease.

CHAPTER 1

Since 1965, the Glasgow Mass Health Examination Unit of what is now the Greater Glasgow Health Board, in association with University Department of Community Medicine, has examined and then followed-up a cohort of approximately 30,000 males and females identified by occupational group or by census of the general population in the west of Scotland. The response rates among those eligible for examination in most of the defined population examined, have been in the region of 80%. All data recorded have been stored on computer for prospective study. Baseline data acquired at the initial examination of each group, have been supplemented and updated by physical re-examination, by postal questionnaire and by medical record linkage for mortality and for migration, through the National Health Service Register of the Registrar General for Scotland and by medical record linkage for morbidity through SHIPS.

It was decided to mount the study in two stages starting in March 1972, to provide experience, test feasibility and validate methods. The then Burgh of Renfrew was selected for the pilot phase for the main study to be mounted later in the Burgh of Paisley. The pilot study in Renfrew was completed successfully in March 1972, and between 1974 and 1976 the Paisley study was conducted. Both populations were to be physically re-examined by 1979. All these events took place as planned and on schedule (15). The middle-age population, which had the highest relative risk of cardio-respiratory diseases, was the target population.

The major motivation in conducting the study is a

continuing need to reduce the risk factors, or conditions predisposing to premature death or disability, ranging from diseases like hypertension which primarily affect the heart and blood vessels of the brain, to tuberculosis and bronchitis which affect the lungs and air passages, by prevention as well as by management of established disease and to eradicate tuberculosis. The cardiovascular and pulmonary systems are intimately associated one with the other; and so the predisposing agents of interest are collectively described as cardio-respiratory risk factors and their outcome as cardio-respiratory mortality. The major diseases under study are IHD, stroke and cancer of the lung and respiratory passages. Together they still represent major epidemics causing premature deaths world-wide in Westernized countries.

1.4-THE RENFREW AND PAISLEY STUDY

1.4.1-Rationale

Diseases of the circulatory system (16) are the leading cause of death in Scotland. In 1972 they accounted for 54.6% of a total mortality, comprising 17,399 men and 18,095 women, to which IHD (16) contributed 10,763 male and 8,238 female deaths representing 32.4% and 24.9% respectively of the national mortality. In the last two decades, the annual increase in IHD in the United Kingdom has been greater than in the United States, but not as marked as in Northern Europe (17,18). A comparison of age-specific death rates in 1969 showed these to be about the same in men and women as in the United States and Finland, but higher than in Czechoslovakia, Singapore, Sweden and

Japan (19).

Cardio-respiratory disease, cancer and tuberculosis in the west of Scotland were known to have a higher prevalence and mortality rate than the rest of Scotland which itself had a higher rate than England and Wales and Western Europe (20,21). The scarcity of epidemiological knowledge of the diseases which did exist was based on the study of mortality statistics, often not very revealing in the investigation of long-term diseases, or on clinical studies. It was felt that the best hope for new insights lay in the study of these diseases in populations of normal composition, including both the sick and the well.

The Renfrew and Paisley Study, therefore, focused on IHD, stroke, bronchitis, cancer and tuberculosis. These were and are the most important causes of mortality and morbidity in the west central Scotland. As a working hypothesis it was assumed that these diseases do not each have a single cause, but that they are the result of multiple causes with a long latent period within the individual.

It was necessary to define the population on which the study would be carried out. Ideally, perhaps, epidemiological investigations of CVD should be set up in a number of widely separated areas simultaneously, so that various racial and ethnic groups will be represented, and a variety of geographic, socio-economic, and other environmental factors can be considered. The results of a study of a single area will be generalisable only insofar as the population of the area is representative of some larger population. Many thousands of persons should be

included to allow for numerous aspects of analysis, and it would be profitable to follow a cohort of individuals from birth to death. Because of the expense of examination and follow-up it was not considered practical to carry on studies simultaneously in several areas, nor to observe directly several thousand people for more than a limited number of years. But the survey team believed that long-term follow-up indirectly through medical record linkage was possible. It was concluded, therefore, that the study should be set up in two areas close to each other with the same socio-economic and ethnic status and population structure; Renfrew was choosen as a pilot study area and Paisley for a definitive study. Coverage was limited to approximately 20,000 persons in the age range 45-64 years. This group would be observed through medical record linkage for morbidity, and with mortality record linkage through the Registrar General indirectly for a long period. This method of follow-up is particularly worthwhile when economy is a prime consideration.

1.5. PRINCIPLES, AIMS, OBJECTIVES AND ORGANISATION OF THE RENFREW AND PAISLEY PROJECT

1.5.1-General principles

The historical background of the project dictated a community approach. It was further felt that, because tuberculosis, cardio-respiratory diseases and cancer were a wide-spread health problem and the risk factors affected a major proportion of the population, the disease should be regarded as a community problem. Accordingly the fundamental principle was to eradicate tuberculosis and

to control cardio-respiratory diseases and cancer in the whole community, as in the control of any epidemic (15).

Currently since many heart and lung diseases are related in both origin and natural course, the measures needed for control also overlap. This also applies not only to cardio-respiratory disease but also to other related chronic disease problems. Thus the programme needed to be comprehensive; it needed to include primary prevention, to strengthen treatment and secondary prevention, and to evaluate the research.

Even though a comprehensive approach was chosen, primary prevention of the disease was emphasised. This was because treatment of the clinical stages of chronic diseases has only limited success. It was considered that this mass epidemic could best be controlled through mass prevention.

Because of the high prevalence and general level of the CVD risk factors, the preventive activity had to be directed towards the whole population. Because risk factors are closely related to lifestyle and environment, the involvement of the whole community was essential. The activity had to be aimed at establishing a healthy environment, changes in health behaviour and comprehensive treatment or avoidance of the risk factors.

Community control of cardio-respiratory disease implies that existing scientific knowledge can be applied to serve the population. Even if continuous efforts for new medical and technological advances are still needed, major steps in the control of cardio-respiratory and related disease are possible by the application of

existing knowledge. Although final proof is lacking -as it may always be- it is important to intelligently apply available knowledge. Carefully evaluated programmes can gradually diminish uncertainty, give information about the consequence of new programmes, and guide decision-making and allocation of resources in this area.

This approach was essential in the Renfrew and Paisley health plan. The concept was to implement the intervention in the form of a systematic and planned programme. The programme content was determined by existing medical, behavioural and social knowledge, and by local factors. Evaluation was by continuous follow-up to guide the programme.

1.5.2.Aims and objectives

The project aim was to carry out a community based health programme to ascertain the prevalence and incidence of tuberculosis over a period of 5 years in these two defined populations characteristic of west central Scotland against the possibility that there might be some additional mass measure like tuberculin testing or sputum examination that could enhance the precision of diagnosing asymptomatic disease and thus hastening eradication. This aim coincided with the need to identify and measure the risks of dying from the chronic epidemic disease, IHD, other forms of CVD, lung and other cancers and chronic obstructive airways disease. All of these conditions cause excess mortality in west central compared with the rest of Scotland and in Scotland compared with England and Wales (20,21).

The main objective was eradication of tuberculosis and to decrease the cardiovascular and cancer morbidity and mortality among men and women aged 45-64 years in Renfrew and Paisley.

To satisfy the main objectives, intermediate objectives were outlined (i.e. those factors that were likely to affect the main objectives). These were based on knowledge about the natural course of CVD and cancer. Changing risk factors could change the rate of the disease. The prevalence of these factors in the target population was considered. Because of the vast task and the complex problems of community intervention, the preventive programme was restricted to smoking and blood pressure factors of strategic importance. The intermediate objectives were:

1.To reduce smoking and high blood pressure among the study population (primary prevention).

2.To promote early detection, treatment of high blood pressure as well as tuberculosis in the community (secondary prevention).

The selection of smoking and hypertenion as risk factors was based on available knowledge from epidemiological studies and recommendations of expert groups and agencies because at the planning stage of the programme, there were many uncertainties about the aetiology of CVD and lung cancer. Changing these factors formed the intermediate objectives for the programme's primary preventive work.

1.5.3-Selection of Community

The adjacent boroughs of Renfrew and Paisley were

selected as the site for this study for several reasons. The population is readily accessible by transportation and communication. Additionally, Renfrew was smaller and was suitable for a pilot study, and for testing and training personnel. The most important step in initiating the study was to obtain support from all local physicians. Support was also obtained from local newspapers and radio and television stations, and particularly, financial support from the King Edward Memorial Trust.

At that time Paisley was the largest Burgh in Scotland. Its population was considered characteristic of that section of Scottish population at highest risk from tuberculosis and other cardio-respiratory diseases.

1.5.4. Community Arrangements for Screening

A programme which involves medical examination of large number of people requires the acceptance, endorsement, and support of the medical profession. The plans for the project were given the endorsement of the Renfrew and Paisley general practitioners. In the Renfrew and Paisley study the general practitioners offered their active support to the programme as proposed. The Royal Alexandra Hospital in Paisley continues a close cooperation with the study.

From an administrative standpoint it was necessary to secure clinical facilities and recruit professional and technical staff. The temporary screening centres were established in a hall or other suitable public meeting place in each of ten sectors of Paisley and in Renfrew and included space for clinical and physical examination as

well as for diagnostic equipment. Staffing was organized which comprised about 30-40 permanent, part-time and voluntary workers from the British Red Cross Society. Numbers varied from month to month according to the changing of the work programme. Additional numbers included an epidemiologist; an examining physician; a programmer; a clinic nurse; X-ray, electrocardiography, statisticians; a secretary, and administrative clerks plus medical, technical and lay trainees.

1.5.5.Geography and Demography

The estimated total population of Scotland in 1972 was 5,235,300. Of these, 1,698,200 lived in the Central Clydeside conurbation (22), in which the city of Glasgow with its population of 861,898 (23) is the major centre of an area with a soft water supply and an excess mortality from CVD and other diseases compared with the rest of Scotland, England and Wales (24).

Renfrew and Paisley are urban communities eight miles West of Glasgow in the South West of Scotland (Map 1.1). These towns have a soft water supply.

The population of Renfrew Burgh at the time of survey was about 19,000; Paisley, the adjacent town, had a population of about 94,800 people. A census of all people between the ages 45 and 64 on January 1972 and resident in the 6,534 households (99.1% response) on the Renfrew Burgh assesor's rating list was completed between November 1971 and March 1972. Information on all but 59 (0.9%) household in Renfrew show that there were 1,788 male and 2,022 females (a total of 3,810 subjects) in this age group.

The population of all people between the ages 45 and

64 in 1973 and resident in the 32,429 households in the Paisley Burgh were about 21,600. Information on all household residents in Paisley showed that there were 10,100 male and 11,500 female in this age group according to the Report of the Registrar General for Scotland 1973. Most of the residents were employed locally in well-established business and manufacturing activities. Medical care was obtained from local GPs, utilizing one NHS hospital near the centre of Paisley.

1.6.SAMPLING PLAN

The choice of sampling plan for this study was dictated by a number of considerations, some of which have already been referred to.

One important decision which had to be reached concerned the age range of the study population. The selection of a middle aged population was for two reasons. First, the middle-aged population is at greater risk of developing cardiovascular disease. Secondly, a very young population would have needed many years to show changes in disease rates. Conversely, among an elderly population with advanced disease the impact of preventive and other control measures would probably be limited. But there were good indications to believe that in the middle aged, preventive intervention could decrease risk within a few years (25). Clearly, if only a very young group was studied, only a very small number would develop cardio-repiratory or cancer even in 10 to 20 years' time and since this is a mobile age group they would be difficult to reexamine regularly or follow through medical record

linkage. On the other hand, in a very old group there would be too large a proportion with pre-existing cardio-respiratory disease and cancer. To balance these two effects, the age group 45-64 was selected for study. Nine hundred and sixty three people beyond this age range voluntarily participated but have been excluded from all analyses throughout this thesis. These people were included in the original sample because it would be desirable not to break up families -that is, if one member of a family was to be brought into the sample, all other family members resident in the same household who wished to participate were also brought in.

1.7.SAMPLE RESPONSE

In Renfrew a total of 3,000 people -1,407 males and 1,593 females- attended for examination in 1972. In 1973, 1,062 (79.6%) males and 1,201 (79.6%) females eligible and capable of attending for re-examination -about 60% of those originally eligible in 1972- returned for examination. In Paisley, 12,446 (77.9% -range 58.4% to 79.4%-) men and women from 15,971 persons eligible and capable of attending for examination attended from the 10 sectors which were examined in that town between February 1974 and June 1976.

At the outset an invitation was issued to all town residents in the age range 45-64 to come to a clinic for examination.

Table 1.1 Shows the response rate for the whole of Paisley and Renfrew and for each of the 10 sectors outlined in the map of the Paisley Burgh. Response varied according to the section of town, which probably

corresponded to differences in socio-economic characteristics. From one sector to another the response ranged from 58.4% to 79.4%. Of the 19,781 persons in the sample who were alive and resident in Renfrew and Paisley at the start of the study, 78% had been tested at the end of the initial examination. In Paisley, a final non-response survey concluded the first round of examination in 1976 and raised the response rate from 74.5% to the more satisfactory level of 77.9%. But still there were about 20% non-respondents and this could result in bias. Non-respondents could include people who felt fit and could not be bothered, people who felt ill, and people who were afraid or unable to attend. However, because of the high prevalence of risk factors found among participants this non-response rate is less likely to be serious.

The reason for non-participation remained unknown in most cases. This means that even after the second invitation the subject did not participate and did not give any reason. A few people were unable to answer. Only one person refused to participate. There were no important differences in attendance rates for men and women, for afternoon or evening sessions, or for different days of the week.

No attempt was made to perform a non-responders survey among the Renfrew or Paisley sample, but a non-responders survey was performed in one of the occupational groups of the Midspan survey (Caterpillar Company) where the response rate was 69.8%. This showed no consistent difference between attenders and non-attenders (26). On

this basis it was considered that the possibility of bias in those coming for the examination was insignificant. However, the possibility of self selection bias cannot be ruled out.

1.8.BASELINE SURVEY FOLLOW-UP

Those people originally examined in Renfrew and Paisley in 1972 to 1976 were followed in several ways to obtain additional information both on the programme effect at the individual level and on the cardio-respiratory and lung cancer risk indicators in the population. These data can be used to analyse CVD risk factors in the target population. The Renfrew cohort were re-examined in 1973 and 1977 and the Paisley cohort in 1979.

One of the problems of cohort studies is maintenance of an adequate response. Although the response rate for both Renfrew and Paisley were of the order of about eighty percent at the first examination, the rates for various reasons, including death and migration out of the study area, reduced responses to as low as sixty percent in some sections of the two cohorts over the five years' interval between the first and second examinations. An expedient developed to overcome this problem and to ensure as complete coverage as possible of the two cohorts for the protracted period of years needed to observe the development of new disease in those originaly healthy, was an indirect method of surveillance called record linkage.

In order to study morbidity in the study population, medical record linkage was arranged with the Scottish Home and Health Department Research and Intelligence Unit. The Western Regional Hospital Board Cancer Registration

Bureau, and the local tuberculosis department. Medical record linkage was established and has been demonstrated between the study cohorts, the SHIPS collected annually by the Common Service Agency in Edinburgh. Written permission was obtained from all but one person to consult his or her health records for this purpose.

In order to study mortality, with the written and witnessed consent of each individual checked, the individual NHS record for that examinee held in the NHSCR of the Registrar General for Scotland in Edinburgh was "flagged". When the individual died or migrated the information was transmitted to the Mass Radiographic Centre in Glasgow so that new events, particularly mortality, could be accumulated at regular yearly intervals and up-dated mortality rates determined. The project collected these data and used them in the evaluation since they were available much earlier than the national mortality data. The original diagnosis of the physician in charge was used to classify the cause of death according to the International Classification of Diseases (ICD) 9th revision.

Up to January 1st 1986, 1,530 male and 1,056 female deaths had been notified by the NHSCR. Fifty four percent of male and forty six percent of female deaths were attributed to diseases of the circulatory system (ICD/9 code 390-459). IHD rates were 40% and 28.6% in men and women respectively. The corresponding figures for stroke were 8.7% and 11% of total deaths in men and women respectively.

The advantages of being able to conduct a long-term follow-up indirectly in this way with relatively little expense and no physical re-examination, recommend themselves especially when economy is a prime consideration.

Using the information collected at the baseline physical examination e.g. level of blood pressure, serum cholesterol, blood glucose, smoking habits, weight and height, and relating these levels or values to mortality, it was possible to calculate risks of different disease mortalities. By comparing mortality in a group within a cohort exhibiting low or "normal" risk variables with groups exhibiting high risk values, a series of risk calculations could be developed, which as the number of deaths accumulate, provides successively more precise estimates of the predictive significance for dying amongst those initially in the "normal" compared with "high" categories.

A special blood pressure clinic was established in the local health centre in Renfrew and in the main hospital of Paisley, staffed for 3 evenings each week by a team of part-time doctors and nurses to undertake the detailed investigation of confirmed cases of hypertension and to initiate and supervise treatment (21).

Subjects with blood pressure in the range 100 to 114 mmHg diastolic are recalled for re-examination. If the blood pressure remains in this range patients are referred to the clinic. At the clinic examinees were re-measured if they remained in the range 100 to 114 mmHg. In the absence of certain contra-indications, they were admitted with

their informed consent and that of their family doctors to the MRC multi-centre trial of "mild" blood pressure (27). At 12 weeks all examinees and their family doctors received a final computer printed report signed and checked by the screening unit doctor.

All subjects with abnormalities needing immediate attention were referred directly to their general practitioner. This group included patients with a DBP of 115 mmHg or more which had been confirmed by two observers. Subjects with DBP between 100 and 114 mmHg were recalled for a second screening examination 12 weeks later. All subjects with other abnormalities had these rechecked and where necessary were referred to the general practitioner or through the general practitioner to hospital. Risk scores for each subject were calculated on a scale derived from the Framingham study (28) and a high-risk group of smokers constituting about 10% of the population most likely to develop IHD, lung cancer and chronic bronchitis were randomly allocated to a controlled trial of the effects of stopping smoking on mortality.

All of the information obtained, except name and other identifiable data, was stored on the University of Glasgow ICL computer. Names and addresses of examinees were stored on a separate magnetic computer tape belonging to the Argyll and Clyde Health Board to preserve individual confidentiality. The data collected on the subjects at baseline and at each follow-up examination were coded on self-coding forms, then transferred directly to tapes for computer analysis.

CHAPTER 2

REVIEW OF LITERATURE

SUMMARY: The aim of this review is to provide information on associations between high blood glucose and morbidity and mortality outcome, gender differential in mortality and use of different indices of blood pressure as predictors of IHD and stroke. The first section of this chapter (2.1) reviews the controversial issues of association between asymptomatic hyperglycaemia and morbidity and mortality and provides some approaches for further investigation. The results of several studies considered together do not indicate an association between asymptomatic hyperglycaemia and IHD that is consistent, strong and graded, while some others did. Also some of these studies do not consistently show evidence for a threshold relationship. Finally, the negative results for some of the studies when multivariate analysis were done (including serum cholesterol, blood pressure, cigarette smoking) raised additional questions about the relationship between asymptomatic hyperglycaemia and IHD.

There have been a few prospective studies of association between asymptomatic hyperglycaemia and morbidity and mortality in women with controversial results which provide hypotheses for further study. There have also been a few prospective studies of association between asymptomatic hyperglycaemia and stroke, the results of which have been controversial. This indicates the need for further study.

The second section (2.2) reviews the gender differential in mortality in general terms with special emphasis on the impact of gender differential in CVD mortality risk. For most causes of death which affect both genders, males register a higher rate than females, a difference which is not completely explained by demographic, psychosocial, behavioural or biochemical differences.

The last section (2.3) reviews the literature regarding the use of different indices of blood pressure as a predictor of IHD and stroke. The relative importance of SBP versus DBP in predicting risk of IHD or stroke is controversial. Recently, for IHD many epidemiological studies favour SBP, while for stroke a few studies favour SBP. This warrants a detailed re-analysis of the various components of blood pressure in relation to IHD and stroke in the west of Scotland.

CONTENTS

2.1.ASYMPTOMATIC HYPERGLYCAEMIA AND CVD

2.1.1.Hyperglycaemia and IHD

The original observations from population studies suggesting a relationship between hyperglycaemia or impaired glucose tolerance, excluding clinical diabetes and coronary heart disease were published in 1965 from two cross-sectional studies from Bedford, England (29), and Tecumseh U.S.A. (30). In the Bedford study an increased prevalence of "arterial" symptoms and ECG abnormalities was observed in subjects with impaired glucose tolerance ("borderline" diabetes) as compared with normoglycaemic control subjects. During a 10-year follow-up, coronary heart disease mortality was higher both in men and women with impaired glucose tolerance than in normoglycaemic control subjects, the relative excess of IHD mortality associated with impaired glucose tolerance being more marked in men than women (31). In the cross-sectional data from the Tecumseh study an increased frequency of impaired glucose tolerance was found in subjects with evidence of vascular disease (IHD, cerebrovascular disease or peripheral vascular disease). In the 7-year follow-up data from the Tecumseh study (32) there was a suggestion of a trend towards an increased incidence of IHD (IHD death or myocardial infarction) in subjects whose 1-hour post-load blood glucose levels at the initial examination were in the upper tertile of the distribution.

In the Framingham study casual blood glucose values were measured instead of carrying out glucose tolerance tests. In the 16-year follow-up data from the Framingham

Study Population casual blood glucose levels showed a non-linear relationship to the incidence of IHD, with a marked increase in the incidence rate at casual blood glucose levels above 120 mg/dl (33). In multivariate analyses of the Framingham 16-year follow-up data, as in other Framingham study analyses (34), it appeared that "glucose intolerance" was related to the incidence of IHD independently of other risk factors, such as blood pressure and plasma cholesterol and cigarette smoking. Previously diagnosed diabetics were included and this increased the predictive value of "glucose intolerance", as defined in the Framingham study.

Fuller et al. (35) compared the impact and interaction of CVD risk factors or indicators in subjects with impaired glucose tolerance and in normoglycaemic subjects. IHD mortality was approximately doubled for subjects with impaired glucose tolerance defined as blood sugar above the 95th centile. A high plasma cholesterol level, cigarette smoking and a low occupational status were not associated with as high a relative risk of IHD death in the impaired glucose tolerance group as in the normoglycaemic group, whereas a high blood pressure and a high BMI were associated with a greater relative risk in the impaired glucose tolerance group. For subjects with ECG abnormalities the relative risk of IHD death was similar in both blood glucose categories, being more than three times those without ECG abnormalities.

The results of subsequently published prospective population studies examining the relationship of glucose tolerance to the risk of IHD have been conflicting. The

best evidence comes from the joint publication of the results from a number of population studies by the International Collaborative Group (36). This joint publication is based on 15 studies in different populations. Each study had measured circulating glucose, obtained an ECG, and assessed a number of variables relevant to cardiovascular status, -relative weight, blood pressure, smoking history and circulating cholesterol. Each had the capacity to follow to death those examined at baseline, 11 studies completed four or more years of such follow-up. For the other four studies, only cross-sectional data are presented. The benefits of such collaboration were several. Mortality follow-up requires either large numbers or many years of observation if meaningful comparisons are to be made. Few individual studies are of sufficient size to accomplish this in a few years.

In nine of these studies participants were employed workers (England, Finnish Policemen, France, Italy, Japan, Switzerland, USA (three studies)). In five studies they were community populations, total or random samples (Australia, Denmark, Finnish Social Insurance and Scotland). An Irish study involved volunteers in a community screening programme.

These studies had not been planned according to a similar protocol and the methods used in the assessment of glycaemia were not similar. In some studies only fasting or casual blood or plasma glucose levels were measured, whereas in other studies oral glucose tolerance tests were

carried out, but again there was a large variation between studies in the timing of blood sampling and other aspects of glucose tolerance tests. The common feature in the jointly published series of papers by the International Collaborative Group was a similar approach to the analysis of data.

Although several studies involved both men and women, data are included for males only, since numerator cases were few for females.

Nearly all the International Collaborative Group studies showed an increased prevalence of ECG abnormalities in the highest blood glucose quintile, and in addition, in those studies with numbers large enough to analyze the upper 2.0-2.5 per cent of the glucose distribution separately, an even more markedly increased ECG abnormality rate was observed in this highest quintile. Blood glucose levels showed statistically significant associations with other risk factors (37). In the majority of these studies, an independent relationship between blood glucose and prevalence of ECG abnormalities did not persist in multivariate analyses.

The results concerning the relationship of blood glucose level to IHD mortality based on 4 to 15 year follow-up periods, are the most important among the results presented in the papers published by the International Collaborative Group. Mortality data were published from 11 different studies, but the results of 9 studies were based on post-load blood glucose values. These studies are: Busselton study from Western Australia (38); Peoples Gas Company study (39), Western Electric

Company study (39), and the Chicago Heart Association Detection Project in industry (40) from Chicago, U.S.A.; Social Insurance Institution's Study (41), and Helsinki Policemen Study (42) from Finland; Whitehall Study (43) from London, United Kingdom; Paris Prospective Study (7) from France; and Basle Longitudinal Study (8) from Switzerland. The other two studies are the Renfrew community study as a part of the Midspan study (44) from Glasgow, Scotland based on casual post-prandial blood glucose determination and the Glostrup population study (37) from Denmark based on fasting blood glucose levels. Comparison of cardiovascular and IHD mortality rates in the highest blood glucose quintile to those observed in the lowest quintile showed that this risk ratio was, for both cardiovascular disease and IHD, greater than 2.0 in only 3 of the 9 studies based on the oral glucose tolerance test (GTT) (Whitehall study, Helsinki Policemen study and Peoples Gas Company study). On the other hand, if in the same 9 studies cardiovascular and IHD mortality in the uppermost end of the blood glucose distribution (highest 2.0-10.0%) was considered, the mortality ratio observed/expected was, for all CVD and IHD, both near to 2.0 or greater in 5 to 9 studies, although in some of these studies this was based on very small numbers of deaths. Multivariate analyses of data from different studies showed that, with one single exception, blood glucose levels did not have a predictive value independent of other risk factors.

It is difficult to explain inconsistencies between

different studies of the International Collaborative Group with respect to the relationship between hyperglycaemia and IHD mortality. One can not, however, exclude the possibility that the failure of some studies to find any association between post-load blood glucose level and IHD mortality could be related to a lesser degree of standardization of the conditions and methods of the oral glucose tolerance test leading to incorrect classification of individuals with respect to glycaemia.

In the Whitehall Study the 7.5 year follow-up data showed that IHD mortality doubled above the 95th centile ($\geqslant$96 mg/dl) for 2-hours post-load blood glucose, suggesting that there would be a threshold phenomenon in the strongly non-linear relationship between blood glucose and IHD mortality (35). In the Paris Prospective Study a similar threshold phenomenon was observed in the relationship between blood glucose and IHD mortality, but at a 2-hours post-load blood glucose of 140 mg/dl (45). In the Paris Prospective Study the incidence of non-fatal myocardial infarction was also analyzed, but blood glucose levels were not found to have any definite relationship to the incidence of this manifestation of IHD (45). In the 9.5 years follow-up data from the Helsinki Policemen Study (46) a non-linear relationship was also observed between fasting, 1-hour or 2-hour post-load blood glucose levels and the incidence of "hard criteria" IHD events (IHD death or non-fatal myocardial infarction). The greatest increase in the IHD incidence occurring above the 80th centile of blood glucose levels. In the Helsinki Policemen Study the rates for both IHD death and non-fatal myocardial

infarction were increased in the upper quintiles of blood glucose levels. In multivariate analyses, however, blood glucose variables were not found to be predictors of IHD risk independent of other risk factors.

In Busselton, Australia (38), the rate of ECG abnormalities in the highest quintile of post-load plasma glucose was twice that observed in the lowest glucose quintile in univariate analyses. In an 11 year mortality follow-up, similar univariate analysis showed no association of baseline glucose value and subsequent coronary or cardiovascular death. When other factors such as age, blood pressure, serum cholesterol, relative weight and cigarette smoking were considered in multivariate analysis, no association between initial glucose level and mortality was seen. As a result of this study, the data do not give evidence that asymptomatic hyperglycaemia was a significant risk factor for mortality in this population aged 40-59. However the number of coronary events used in this study was small and caution is required in drawing conclusions.

In the Glostrup, Denmark study (37), based on fasting blood glucose levels, no positive association between baseline glucose level and ECG abnormalities was found, either in univariate analysis or in multiple logistic analysis. A significant positive association between blood glucose and blood pressure, resting heart rate, serum triglycerides and BMI was found in this study. In a 10 year follow-up, baseline glucose levels were not found to be predictive of mortality or of combined fatal and non-

fatal cardiovascular events. As a result, in this study asymptomatic hyperglycaemia based on fasting blood glucose was not associated with higher incidence of CVD. Of course again the number of cardiovascular deaths is relatively low to draw any strong conclusions.

In the Social Insurance Institutions's Study, Finland (41), the 1-hour post-load plasma glucose, in males aged 45-59 years, showed a linear and partly independent relationship to ischaemic ECG abnormalities. During a 4 year follow-up, the 1-hour post-load plasma glucose level had no relationship to total mortality or to mortality from CVD or IHD.

In the Renfrew community study (44) blood glucose levels were measured in 1,134 men aged 45-64 in 1972, and these were followed for 6 years to determine mortality rates. A positive association was found in univariate analysis, between the baseline glucose level and the prevalence of ECG abnormalities as defined by nearly all the International Collaborative Group Studies. In multivariate analyses of these cross-sectional data, an association was seen for Whitehall but not Pooling project abnormalities. No association was found between asymptomatic hyperglycaemia and coronary mortality at 6 years, either in univariate, bivariate or multivariate analyses. Of course, the sample size was small and mortality data was based on a very small number of deaths.

In the Basle Longitudinal Study (8) from Switzerland, no consistent association between baseline glucose and resting ECG endpoints either in univariate or multivariate analyses was seen. In this study the

frequency of peripheral artery disease was also analysed, and was negatively associated with glucose elevation. In a 5-year mortality follow-up too few deaths from coronary disease occurred to permit any conclusions on long term risk of hyperglycaemia. However, the available data did not show a positive association of mortality with glucose level.

In the Chicago Western Electric Company study and Chicago Peoples Gas Company study (39) from USA, in univariate analysis, those at the highest glucose levels had a higher rate of ECG evidence of IHD, but this association in multivariate analysis, when such factors as age, blood pressure, weight, cholesterol and cigarette were taken into account, did not remain. These long-term follow-up mortality studies (10, 13 and 15 year) showed inconsistent findings on the association of hyperglycaemia and subsequent death. In one cohort (Gas Company men followed for 10 year after a 1-hour post-load glucose determination) a positive glucose-mortality association was found in both univariate and multivariate analysis. But in the two remaining cohorts (Gas Company 13-year after casual glucose determination and Western Electric 15-year after 2-hour load determination) no such association was found. While differences in the method and sample size as well as other limitations may have contributed to the differences observed, the inconsistency of the findings do not permit a conclusion that asymptomatic hyperglycaemia is a positive coronary risk factor.

In the Chicago Heart Association Detection Project in Industry (40) from USA, a cross-sectional analysis of the frequency of ECG abnormalities showed that those in the upper 2.5% of glucose distribution had higher rates of such abnormalities than the rest of the group. Men in the highest quintile likewise had higher rates of ECG abnormalities than were seen in the lowest quintile. MLR analysis showed an inconsistent positive association of glucose with prevalence of ECG abnormalities but no association with definite MI, on ECG. In the 5 year mortality follow-up, while men with overt diabetes experienced coronary death rates 2-3 times higher than those without such a diagnosis, similar univariate analysis that excluded diagnosed diabetics showed no association between initial glucose and subsequent coronary or CVD mortality, although all cause mortality rates were significantly related to glucose levels. The inconsistent results between univariate and multivariate analyses, as well as between cross-sectional and prospective findings, do not support a conclusion that asymptomatic hyperglycaemia is a major coronary risk factor.

In four of the Collaborative studies the mortality follow-up was not performed (Denmark 40-year, Ireland, Italy and Japan) but the results of cross-sectional studies are as follows: The study of the Republic of Ireland (47) included volunteers in a community screening programme. After a 1-hour 50-g oral glucose load in univariate analysis no linear relationship between hyperglycaemia and ECG abnormalities was observed. In

multivariate analysis, considering also age, SBP, relative weight, serum cholesterol and cigarette smoking, no independent association was seen between glucose levels and frequency of ECG abnormalities.

In the Olivetti Survey, Italy (48) no association was seen between initial fasting blood glucose level and ECG abnormalities using the criteria of the Whitehall study. However, there was a positive association between baseline glucose and ECG abnormalities defined by the US Pooling Project. These associations were also evident in multivariate analyses.

In Japanese National Railways Workers (49), in both univariate and multivariate analyses, an association between ECG abnormalities and IHD was seen.

In the Glostrup population study (3), both fasting glucose and 1, 2 and 2.5 hour glucose after an oral load in forty-year old men showed no consistent relationship between glucose variables and resting ECG abnormalities. For post-exercise ECG abnormalities, all glucose variables showed a positive association both in the univariate analyses and in the multivariate analyses and the 1-hour post-load glucose values were significantly correlated to the prevalence of post-exercise ECG abnormalities independent of other risk factors for IHD, such as SBP, cholesterol, BMI, and cigarette smoking. A significant positive correlation was found between all four serum glucose variables and BMI, SBP, DBP and serum uric acid.

2.1.2.Hyperglycaemia and Cerebrovascular Disease

The epidemiological studies of association between

high blood glucose values and stroke mortality and morbidity are scant. Analyses of the Framingham study concerning the relationship of casual blood glucose levels, including previously diagnosed diabetics, to the incidence of atherothrombotic brain infarction (ABI) suggest that this relationship is curvilinear, with a more marked increase in the incidence at the upper end of the blood glucose distribution (50). In the Whitehall study population the relationship of stroke mortality and impaired glucose tolerance, as defined by 2-hour post-load blood glucose levels at the initial examination, was analyzed on the basis of 10-year follow-up data (51). No trend of stroke mortality was found below the 90th centile for 2-hour blood glucose (<90 mg/dl), but the stroke mortality showed an increase in the 90th-95th centile range and was doubled above the 95th centile (2-hour blood glucose from 97 mg/dl to 200 mg/dl). Multivariate analysis showed that a blood glucose level above the 95th centile was a risk factor for stroke mortality, independent of blood pressure, plasma cholesterol, smoking and obesity.

2.2.GENDER DIFFERENTIAL IN MORTALITY

The earlier work suggests that cultural, behavioural and biological factors contribute to the longer life expectancy of women (52).

Wingard (53) examined the gender differential in mortality risk in Alamada County, California after a nine year follow-up, while simultaneously controlling for 16 demographic and behavioural risk factors. Risk factors included age, race, socioeconomic status, occupation, physical health status, use of health services, smoking,

alcohol consumption, physical activity, weight, sleeping patterns, marital status, social contact, church and group membership and life satisfaction. These demographic and behavioural risk factors do not account for the overall gender differential in mortality rates. In a later study Wingard et al. (54) added biological variables. The risk factors included age, marital status, education, cigarette smoking, cholesterol, SBP, fasting plasma glucose, and obesity. These risk factors explain a good portion of the gender differential in mortality from all causes. However, this study indicates that a substantial gender differential remains in heart disease mortality after adjustment.

Waldron (55) reported that the largest differences between male and female death rate occur for IHD, accident, suicide, lung cancer and cirrhosis of the liver. She suggests that these causes of death are linked to patterns of behaviour which are encouraged or more accepted in males (e.g. smoking, drinking alcohol and working in hazardous jobs).

The total pathological effect of smoking, particularly the elevation of IHD, lung cancer and emphysema, makes a major contribution to the gender differential in total death rates. Retherford (56) estimates that as much as half of the gender differential in life expectancy from the ages of 37 to 87 may be due to the effects of higher rates of cigarette smoking in men.

Burbank (57) reported that changes in the male and female lung cancer death rate in the United States

parallel changes in male and female smoking patterns. Burbank was able to adjust only for age, while it is known that smoking is also correlated to socioeconomic status (58) and alcohol consumption (59), factors also related to increased mortality risk.

Hammand (60) and Johnson (61) have also examined the gender differential in relation to smoking behaviour. Utilizing data from the American Cancer Society, Hammand (60) adjusted only for age, concluding that smoking is a risk factor for both genders but more so for men. Using Framingham data, Johnson (61) adjusted for age and several biological measurements (e.g. blood pressure and cholesterol), and similarly concluded that IHD mortality for male smokers is considerably higher than for female smokers. Adjustments were not made for factors such as socioeconomic status and alcohol consumption.

Genetic factors apparently also contribute to higher male mortality, although the evidence for this is not as strong as commonly has been believed. Relatively few studies have explored the possibility that women live longer than men because they are biologically more fit than men. A few studies have noted that the male death rate is higher even in prenatal life and infancy (62-64). Since behavioural factors that increase mortality risk do not vary by gender of the foetus, gender differences in the rate of miscariage, stillbirth and early infant death are presumably due to unspecified biologic factors. Males have a higher mortality than females in many different species, and this has been cited as evidence for a genetic contribution to the higher mortality of men (65). However,

although higher male mortality is widespread among insects, other Arthropoda and fishes (65), higher female mortality appears to be just as common as higher male mortality among our close relatives, the birds and mammals (65-67). Among humans, higher female mortality is also common at certain ages, between one and forty and in some cases at older ages in many non-industrial countries (68). However, it is striking that, wherever statistics are available, males have had higher mortality during the first year of life (69). Males also have been found to have higher foetal mortality in most studies (69), although foetal mortality during late pregnancy is as high for females as for males in twins of opposite gender (70), in multiple births of triples or more (64), and in a few geographic areas, for example Scotland (63). Male mortality is higher for many different causes of death. Several authors (65, 71) have inferred from these observations that genetically determined metabolic differences may contribute to the higher mortality of males.

Another study which has been cited widely as evidence of the importance of genetic factors is Madigan's (72) comparison of life expectancy for Roman Catholic Sisters and Brothers in teaching orders. Madigan found that the differential in life expectancy between Sisters and Brothers has been almost as large as the differential between women and men in the general population, even though the Sisters and Brothers had more similar adult roles. However, the higher mortality of Brothers cannot be

attributed solely to genetic causes, since the Brothers smoked and drank more than the Sisters and probably were socialized differently as children, and each of these differences would contribute to higher male mortality.

Most previous discussions of the gender differential in IHD have focused primary attention on the hypothesis that this gender differential is a result of the physiological effects of the gender hormones. The evidence for this hypothesis is suggestive, but it is ambiguous and inconsistent. Castration of men apparently does not reduce deaths due to CVD (73), and castration of older men does not seem to reduce arteriosclerosis (74). Gerther and White (75) suggest that androgen levels of male coronary patients do not differ from androgen levels in a control group. Thus male hormones do not appear to increase the risk of IHD. Do female hormones lower the risk of IHD? Several studies have found that oopherectomy of young women is associated with increased artherosclerosis and IHD (76-80) but other studies have not found this (81, 82). One investigation with negative findings is particularly interesting because women with a simple hysterectomy were used as the control group and the prevalence of arteriosclerotic heart disease was as high for those women with only their uterus removed as it was for women whose ovaries had also been removed (81). For both groups the prevalence of arteriosclerotic heart disease was higher than the prevalence for the general female population. Since there appears to be no physiological reason why the simple removal of the uterus should lead to increased IHD (81, 83), these observations suggests that hysterectomy

may be associated with behavioural characteristics, such as cigarette smoking, or physiological characteristics such as anxiety and neuroticism (84), which in turn are associated with elevated risk of IHD (85).

Thus, if we tentatively accept the weight of evidence as indicating that oopherectomy of young women is associated with increased atherosclerosis and IHD, we still are left with the question of whether this increase is due to the removal of females' hormones or to some behavioural or psychological characteristic of women who undergo these operations. Studies of the effect of replacement therapy are the ideal method for resolving such questions, but in this case such studies have yielded conflicting results. One study of oestrogen therapy in castrated women found a decreased prevalence of arteriosclerotic CVD (80), and another found trends suggesting a reduced prevalence of electrocardiographic (ECG) abnormalities (86). However, a third study found no effect on death rates or prevalence of IHD (81). Furthermore, most studies of oestrogen therapy in men have found an increased risk of recurrence of myocardial infarction (74, 87-89), although in two studies, some treatment groups appeared to have a reduced risk (76, 87). In adults, a possible biological basis for the gender differential in mortality has been examined through the relationship of hormonal status and IHD. These studies (90, 91) reported that IHD mortality increases among women around the age of menopause and varies by pregnancy history, suggesting that changes in oestrogen or prolactin

levels may be the cause. However, increased mortality and morbidity among those receiving supplemental oestrogen does not support this hypothesis (92, 93). Heller and Jacobs reported that women do not lose protection from IHD after menopause (94). They suggested male gender hormones may be risk factor for IHD.

It is possible that behaviour patterns may make a larger contribution to the risk of IHD than does gender per se. Both Haynes et al. (95) and Waldron et al. (96) reported that Type A behaviour is more prevalent among men. Using Framingham data, Haynes et al. (95) reported that 50% of the men in their sample and 38% of women are Type A. Therefore, adjustment for Type A behaviour would probably lower the gender differential. But Haynes et al. (95) also reported that the relative risk of IHD (fatal and non-fatal) associated with Type A behaviour is actually higher for women than for men. These data suggest the hypothesis that men have more IHD than women is in part because Type A is more prevalent among men. Housewives may be even less likely to be Type A than employed women (97). Agressiveness and competitiveness are two key components of the Coronary Prone Behaviour Pattern. Maccoby and Jacklin (98) concluded that on average, males are more aggressive and competitive than females.

Why do males develop more aggressiveness and competitiveness than females? Genetic factors make some contribution to the gender differences in aggressiveness (98), but the extent of aggressiveness among males varies enormously, depending on child-rearing and cultural

conditions (99). Gender differences in competitiveness are fostered by parents and schools who push boys to achieve in the occupation world and girls to seek success in the family sphere (98, 100-102). Occupational achievement apparently requires competitiveness, since in industrialized societies there are seldom as many jobs as there are people who want and can do them. In the family sphere, on the other hand, warmth and love are believed to be much more appropriate and aggressive competitiveness much less appropriate than in the business world (101). Evidence that cultural pressures and expectations do have a substantial influence on the development of the Coronary Prone Behaviour Pattern comes from the observation that this Behaviour Pattern rarely develops in the social environment of many non-industrial societies (99, 103).

Bengtsson et al. (104) in their study of gender differential in IHD in 50-54 year old Swedish women and men conclude that men's higher rates of IHD are related to their higher rates of smoking and drinking alcohol, higher aggressive and achievement scores and greater self-reported stress. These authors believe that additional factors also contribute to the observed gender differences in IHD mortality.

The gender differential in mortality also varies for different groups. For example the excess of male mortality is lowest among married and highest among divorced adults (105). The excess of mortality for un-married males is particularly large for causes like cirrhosis of the liver which are strongly influenced by behaviour, and for

diseases like tuberculosis in which health habits and care play an important role. Gove (105) has argued that the major reasons why the gender mortality differential is higher among males who are not married are that men do not adjust as well as women do to being unmarried, and that men derive greater advantages from being married, both in care received and in psychosocial well-being.

The gender differences observed may depend only on various distributions of the primary risk factors in the female and male populations, which to some extent is supported by findings from previous studies (106-108). In the Framingham study, at least as large logistic coefficients were reported for women for blood pressure and serum cholesterol, but for cigarette smoking this was found only below age 50 (106-108). It has been suggested that high serum cholesterol might not be as strong a risk factor in women as in men, while high serum triglycerides might be an important risk factor in women contrary to the finding in men (106). In the Johansson et al. study the frequency of current smokers was the only primary risk factor that showed a consistently higher prevalence in male compared with female patients (109). This finding has been supported by the Dick and Stone (110) study and may contribute to the male preponderance in the incidence of myocardial infarction.

The San Francisco-Oakland Study (111), which combined blood pressure, cholesterol and glucose levels, weight and ECG measurements into one variable -'IHD Risk Factors'- found a higher relative risk associated with these biological measurements for men than women.

2.3.BLOOD PRESSURE AS A PREDICTOR OF IHD AND STROKE

3.3.1.Blood Pressure as a predictor of IHD

The relative importance of SBP versus DBP in predicting risk of IHD is controversial. This viewpoint has been considered and a number of studies have found that SBP is a better predictor of IHD than DBP (108, 112-120) although this is not a universal finding (121, 122, 123).

Rosenman et al. (119), in the Western Collaborative Group Study of employed men aged 39-50 years, found the risk of IHD was more strongly associated with SBP than DBP.

Lichenstein et al. (120) also compared SBP and DBP as predictors of death due to IHD in male civil servants, aged 40-64 years in the Whitehall study. They found SBP as a better predictor of IHD mortality than DBP.

Kannel et al. (115) compared the contribution of SBP versus DBP of risk of IHD and role of MAP, PP and systolic lability in Framingham study. Assessment of the net effect of each indicates a stronger association of SBP than DBP, MAP or PP with risk of IHD.

Aagetverdal (122) compared SBP and DBP as a predictor of IHD mortality in Norwegian men aged 35-49. He found DBP as a better predictor and suggested that the relative predictive strength of SBP and DBP may depend on age.

The relative importance of SBP versus DBP in predicting risk of IHD was also studied by Rabkin et al. (124), in the Manitoba study. DBP showed a stronger association at the earlier examinations, whereas SBP was more important when the majority of the cohort was between

40-50 years of age. They suggested that in middle-aged men the risk of IHD was more strongly associated with SBP than DBP.

2.3.2.Blood Pressure as a predictor of Stroke

The relative importance of SBP versus DBP in predicting risk of stroke was compared in Manitoba study by Rabkin et al. (124). They found a stronger association with stroke for SBP compared to DBP.

Kannel et al. in the Framingham study also compared various components of blood pressure, including SBP and DBP, PP, lability of pressure, MAP and tension-time index in relation to ABI (125, 126). They stated, while all measures were associated with ABI incidence, that the simple casual SBP emerged as good a predictor of ABI incidence as any other component of blood pressure.

Evans (127) in his pathologic study of blood pressure found a stronger association of SBP than DBP with cerebrovascular disease.

In summary, as indicated by the literature review, the associations between asymptomatic hyperglycaemia and morbidity and mortality, as well as gender differential and its relationship with other CVD risk factors, are controversial. The gender differential in mortality is not completely explained by demographic, psychosocial, behavioural or biochemical differences between the genders. The relative importance of SBP versus DBP in predicting risk of IHD or stroke is debatable and provides a potential hypothesis for further studies.

CHAPTER 3

STUDY DESIGN

SUMMARY: The study can be roughly divided into three stages:

First, to evaluate the use and performance of a register of a well (middle-aged) population (the Midspan Study) for longitudinal studies. The aim of this section is to give a comprehensive and balanced picture of how the project was formulated, implemented and evaluated.

Second, variation in mortality risk is examined among men and women while adjusting for seven CVD risk factors in a series of age-adjusted and MLR analysis. To test a series of specific hypotheses relating to:

1) The measurement of trends in and the determinants of all causes mortality, and mortality from CVD, IHD and CVA in asymptomatic hyperglycaemia (Chapter 6).

2) The extent to which asymptomatic hyperglycaemia interacts with other known cardiovascular risk factors (age, gender, SBP, DBP, serum cholesterol, BMI and cigarette smoking habit) in the prediction of mortality (Chapter 6).

3) Differences in mortality rates for asymptomatic hyperglycaemia and associated risk factors by gender (Chapter 7).

4) The interaction between blood sugar value and BMI in the prediction of CVD mortality (Chapter 8).

5) Gender differentials in mortality (Chapter 9).

6) The use of different indices of SBP and DBP as predictors of IHD and stroke mortality (Chapters 10 and 11).

7) Trends in overall and stroke mortality in Scotland since 1950 (Appendix D).

Third, to determine the feasibility of following up a cohort, through record linkage using the Midspan registry, CHI and general practice records (Chapter 12), and to examine baseline high blood glucose as a possible risk factor for the later development of overt diabetes (Chapter 13).

CONTENTS

CHAPTER 3

3.1.OVERALL DESIGN

This study focused on the use and evaluation of a well population register in the study of all causes, CVD, IHD and stroke mortality and associated risk factors, and the association between asymptomatic hyperglycaemia and later development of overt diabetes. However, the study can be roughly divided into three distinct stages:

First, description of the general aims and objectives of the project as well as the background of the study and evaluation of the use and performance of a register of a well (middle-age) population for longitudinal study.

Second, a series of investigations related to mortality from all causes, CVD, IHD and stroke. These were: how the gender differential in mortality is influenced by seven cardiovascular risk factors; how asymptomatic hyperglycaemia influences all causes, CVD, IHD, and stroke mortality and their gender differential; what is the relative importance of SBP, DBP and different indices of them as a predictor of IHD and stroke mortality.

Third, an evaluation of how a cohort study could be followed indirectly through medical record linkage for mortality and morbidity without physical re-examination. For this purpose individuals with asymptomatic hyperglycaemia at baseline have been followed through record linkage using the Paisley registry and CHI, to examine asymtomatic hyperglycaemia as a possible risk factor for the later development of overt diabetes.

3.2.HYPOTHESES TESTED IN THE STUDY

In this thesis a series of hypotheses were developed. The task of the present study was to attempt to prove these hypotheses. These hypotheses are presented in this section, along with some of the detailed considerations to be discussed in subsequent chapters. However, The following chapters discuss and answer the basic questions:

Does an initial high casual blood glucose level itself constitute a risk factor for all causes, CVD, IHD and stroke death? Does it do so independently of other well-established major CVD risk factors such as high blood pressure, high serum cholesterol level, obesity and cigarette smoking? Chapter 6 examines whether blood glucose is associated with mortality outcome. This analysis compares the age-adjusted ratio of quintiles and percentiles of mortality rates before and after adjustment for confounding variables. They involve quintile and correlation techniques for univariate assessment, bivariate, cross-classification analyses and regression techniques for multivariate analyses.

Do men with high casual blood glucose value have higher mortality rates than women with high blood glucose level? Chapter 7 focuses on whether asymptomatic hyperglycaemia displays the gender differences as found in diabetes or the mortality rates found in general population independent of established major CVD risk factors. This discussion begins by determining whether asymptomatic hyperglycaemia defined by the upper 5% of blood sugar distribution is associated with mortality, noting the differences in the relative mortality risk for men and

women and ends by comparing the distribution of the high blood glucose level among men and women. If asymptomatic hyperglycaemia is both associated with mortality and distributed unequally among men and women, that factor may be masking or enhancing the gender differential in mortality rates.

In this study, how does adjustment for CVD risk factors influence the gender differential in mortality in persons with high casual blood glucose compared to individuals with low blood glucose value? This analysis compares the age-adjusted ratio of male to female mortality rates, before and after adjustment for potentially confounding variables. These adjustments are accomplished through the MLR analysis. The interaction between blood glucose level and SBP, DBP, BMI and cigarette smoking, age and gender was examined through application of the interaction term between blood glucose and other confounding variables in the MLR model.

Chapter 8 covers whether the strength of the relationship between the degree of glycaemia and mortality is independent of weight. These analyses were completed through a set of quintiles analyses, bivariate cross-tabulations and multivariate analyses.

Might the CVD risk factors be a confounding variable for an examination of the gender differential in overall and CVD mortality? Chapter 9 covers whether the variable is associated with mortality and if so, whether it appears to be unequally distributed among males and females and if the mortality risk associated with that variable is

different for men and women. If a variable is both associated with mortality and distributed unequally among men and women, that factor may be masking or enhancing the gender differential in mortality rates.

How does adjustment for these variables influence the gender differential in mortality? This analysis compares the age-adjusted ratio of male to female mortality rates, before and after adjustment for potentially confounding variables. These adjustments are accomplished through the MLR analysis.

Does SBP predict IHD and stroke mortality better than DBP or other indices of SBP and DBP? Chapters 10 and 11 cover whether the SBP predicts IHD and stroke mortality better than DBP alone or other combinations of SBP and DBP, and if so, whether they are independent of other CVD risk factors. We also wish to assess the strength of SBP and DBP as predictors of IHD and stroke mortality to see if it is different between males and females. How does adjustment for other CVD risk factors influence the predictive strength of SBP and DBP and other indices of SBP and DBP in mortality from IHD and stroke? These adjustments are accomplished through univariate, bivariate and multivariate analyses.

In chapter 12 the feasibility of follow-up of a cohort, through record linkage using the Paisley registry, CHI, patients and GP's records, was examined. This part of the study began by determining the feasibility of record linkage between the cohort and CHI to access the last known address and GP's name and address of the baseline examinees in the Paisley study, and ends by attempting to

contact them, as well as their GP, through combinations of mailing and telephone enquiries.

Is initial high casual blood glucose level associated with later development of overt diabetes? To what extent does the presence or absence of an arbitrarily defined high single casual post-prandial blood glucose level play a role in the prediction of diabetes mellitus? How important are BMI, blood pressure, serum cholesterol and cigarette smoking in influencing later development of frank diabetes? Is there any gender difference between the presence of risk factors and later development of diabetes? In Chapter 13 attempts are made to clarify these questions by means of univariate, bivariate, life-table techniques and multivariate analyses.

Finally, have stroke mortality rates, overall and sub-divided by age and gender, changed in Scotland? If so, are they independent of the decline in overall mortality? If this is the case, what are the possible explanations? Is there any geographical variation in decline of stroke mortality in Scotland? Appendix D covers the secular trends in all causes and stroke mortality in Scotland during the period of 37 years from 1950 through 1986 based on age-specific and age-standardized death rates, using official data published by the Registrar General in Scotland. This secondary data analysis is put in a separate appendix rather than kept within the body of the study, to preserve consistency throughout the thesis.

CHAPTER 4

POPULATION AND METHODS

SUMMARY: This chapter provides a description of the study population and general methodology used in the present study. In 1972-76, 10,541 men and women aged 45-64 were recruited in a well-population study (MIDSPAN) of cardio-respiratory disease and risk factors. In this study during a mean follow-up of 11.6 year (Renfrew 1972 to 1986 and Paisley 1974 to 1986), 1,632 deaths occurred among which 794 (48.6%) were of cardiovascular origin, 518 (31.7%) due to IHD and 159 (9.7%) due to stroke. All participants were offered an appointment to attend a temporary examination centre established in the town. Before attending, each patient was asked to complete a standard questionnaire. Individual questionnaires were checked , height, weight and blood pressure were measured. A 10-ml non-fasting blood sample was taken for plasma cholesterol, and blood sugar. The baseline examinees were followed through flagging with NHSCR for mortality outcomes and through record linkage using the CHI and GP records for survivors. Univariate, bivariate and multivariate logistic regression analysis was performed.

CONTENTS

CHAPTER 4

4.1. INTRODUCTION

Because of different analytical features in various sections of this study, this chapter will concern itself with the general principles of statistical analysis. Further details of the statistical analyses used in each individual chapter will be discussed in the chapter concerned if required.

The data presented in this report are based on information gathered by Professor VM Hawthorne and his team in the Renfrew and Paisley study. The population sampling frame of Renfrew and Paisley have been described in detail in Chapter 1. In this chapter the sampling frame used in this thesis is described.

4.2. POPULATION

Subjects: In 1972, during 15 days in March and April a pilot study was completed in Renfrew Burgh. There were a total of 1,366 men and 1,548 women in the age group 45 and 64 years who participated in the pilot study.

In 1973, Paisley was divided into 10 sectors, each of which was examined in turn between February 1974 and January 1976 by the mass health examination unit. There were a total of 5,603 men and 6,691 women in the age group 45 and 64 years who participated in the study.

Briefly, the population of this cohort study comprised 6,969 men and 8,239 women in Renfrew and Paisley combined, aged 45-64 years old when they accepted a general health examination between 1972 and 1976; in this thesis they have been followed-up to January 1986 for mortality. Table 4.1 shows the baseline survey, by area, age and gender.

Because blood glucose data were not collected in the first three sectors of Paisley town and missing values in other variables 4,667 men and women were excluded with incomplete blood glucose or missing data leaving a group of 10,541 men and women for study. Among 10541 men and women on the date of screening 126 (1.2%) were known diabetics (also, 5 cases failed to respond). Since interest in Chapters 6, 7, and 8 centres on apparently asymptomatic hyperglycaemia, and also in Chapter 9 because of well-established gender differential in mortality in diabetics, these men and women were not included in these chapters (Table 4.2). However, available data on diabetics are presented separately in Chapter 6, to complete the description. Information on diabetes status was obtained from the personal history reported by the study participants. Thus, definition of diabetes in this report differs from that in some other epidemiological studies because it is based entirely on a personal history of diabetes and was independent of current blood glucose determinations. Thus, the remaining 10,410 men and women provide data for the Chapters 6, 7, 8 and 9.

4.3.EXAMINATION

In each sector being studied a temporary screening centre with a layout similar to that in Figure 4.1 was established in a hall or other suitable public meeting place. Then timed appointments were issued to all residents between the age of 45 and 64 years identified by the census as living in the sector. Before attending, each patient was asked to complete a standard questionnaire on

symptoms of cardiovascular and respiratory disease and diabetic status. The questionnaire contained demographic data and previous disease, information on bronchitis, smoking habits, drinking habits, amount of physical activity undertaken at work and during leisure, cardiovascular and respiratory symptoms, behavioural characteristics and diabetes mellitus (Appendix A). Ten subjects arrived every 10 minutes during each session. Individual questionnaires were checked for missing information and any doubts expressed by the examinee regarding the questions were resolved and standard investigations lasting about 20 minutes were undertaken.

4.3.1.Smoking Habits

Smoking was measured by a set of questions recommended by the Medical Research Council (MRC) (128) and shown in appendix A. Those subjects who reported that they smoked regularly at the time of examination and smoked more than 5 cigarettes a day on average, were classified as current cigarette smokers.

4.3.2.Weight and Height and Body Mass Index

Weight was measured in indoor clothing and without shoes to the nearest kilogram using a clinical balance scale. Height was measured to the nearest centimetre without shoes.

Adiposity was expressed as BMI which was calculated for each person as weight in kilograms divided by the square of height in metres. The ratio is calculated to two decimal places.

4.3.3.Blood Pressure

Systolic and diastolic readings have been expressed

in millimetres of mercury on the manometer scale. Blood pressure was taken by a trained nurse when the subject was seated with his left arm at heart level, and was measured using the recommendations of Rose and Blackburn (129). Before carrying out the field work observers were trained, the major emphasis being on the theory and practice of blood pressure measurement. Blood pressure was measured using the London School of Hygiene and Tropical Medicine Sphygmomanometer (130), in this apparatus, pressure is raised and lowered automatically at a constant rate of 2 mm/sec when using a standard cuff of 12x22 cm. The machine has three mercury columns controlled blindly by the observer to prevent confusion between aural and visual signals and to reduce bias due to digit preference. The mean of two readings was taken. DBP was taken at the disappearance of the fifth Korotkoff sound. Observers had been trained to measure blood pressure using a special tape recording in order to reduce bias and observer variation (131). Digit preference in collaborating centres was monitored by the MRC computer estimating the rates of terminal zeros being reported by observers in different centres.

4.3.4.Blood Sugar and Serum Cholesterol

The amount of glucose present in the subjects' whole blood and amount of cholesterol present in the serum of the subjects' blood, in milligrams per 100 millilliters, in Renfrew and in millimoles per litre in Paisley was measured. To ensure compatibility between the two areas, the Paisley measurement units were converted to milligrams

per 100 millilitres using the conversion coefficient of 18 and 38.6 for blood glucose and serum cholesterol respectively.

Conversion Factors

Blood sugar, 1 mg/dl=0.056 mmol/l

Serum cholesterol, 1 mg/dl=0.026 mmol/l

A 10 ml. non-fasting blood sample was taken for plasma cholesterol, electrolytes, urea and blood sugar. Blood samples were collected in the afternoon and evenings. Blood samples were collected from the antecubital vein without venous stasis and plasma total cholesterol measured by an autoanalyser technique (132). Glucose was determined (using whole blood) by a measure of oxygen consumption (133).

4.3.5.Vital Capacity

A nurse or technician measured the subjects vital capacity by getting the subjects to take the deepest breath possible and exhale to the fullest extent into a tube of a water-sealed spirometer in one second (Gathur Vitalometre (134)) with the subject standing. Two trials were made for each subject and the highest reading was recorded. This measurement of vital capacity was read to the next lower 0.1 litre on the scale of the spirometer. No adjustment was made for possible variation in room temperature.

4.3.6.Electrocardiogram

An electrocardiogram was made at the baseline examination with the subject in a sitting position. A six

lead electrocardiogram (lead I, II, III, aVR, aVL, and aVF) on the three channel Minograph 34 was made and tracing was subsequently classified according to the Minnesota code criteria (129).

4.3.7.Chest X-Ray

Postero-anterior and left lateral 70 mm. miniature chest X-ray were taken in the standing position. A tuberculin Tine test (Lederle) was made and sputa collected for direct examination and culture as part of the study of tuberculosis.

The cost of the health examination was £4.31 per person in 1972 and £6.39 in 1976.

4.4.BLOOD PRESSURE COMPONENTS

The parameters of blood pressure examined in the prediction of IHD and stroke mortality in Chapters 10 and 11 included: SBP, DBP, PP (SBP - DBP), MAP (DBP + one-third the PP) and MAI (one-third DBP+ two-thirds SBP).

4.5.MORTALITY FOLLOW-UP

In order to study mortality in the whole population individuals were "flagged" with the NHSCR for Scotland in Edinburgh.

Following this survey, mortality data were collected for the 10-14 (mean 11.6) years from 1972-76 to 1986. In this study deaths are reported monthly by the NHSCR in Scotland. Cause of death was classified using the Eighth Revision (1972 to 1978) and the Ninth Revision (1979 to 1986) of the International Classification of Disease, Injuries and Cause of death (ICD) (135). The comparability ratio for the change of classification from the Eighth to Ninth Revision used in this analysis, was estimated as

1.04, 0.93 and 1.04 for CVD, IHD and CVA mortality respectively by the Registrar General in Scotland (136). Causes of death were ascertained from copies of death certificates and grouped into:

1- All mortality

2- CVD mortality (ICD-9 codes 401.0-453.9: heart disease plus cerebrovascular disease, rubrics 430-438, plus hypertensive disease rubrics 401-404, plus arterial disease, rubrics 440-453).

3- IHD mortality (ICD-9 codes 410.0-414.9: acute myocardial infarction, angina pectoris, chronic IHD).

4- CVA mortality (ICD-9 codes 430.0-438.9: subarachnoid haemorrhage, intracerebral haemorrhage, other and unspecified intracranial haemorrhage, occlusion and stenosis of precerebral arteries, occlusion of cerebral arteries, transient cerebral ischaemia, acute but ill-defined cerebral disease, other and ill-defined cerebrovascular disease, late effects of cerebrovascular disease).

In this study CVD deaths are analysed globally, because of the well-known limitations of the accuracy of death certificate data with regard to the various manifestations of CVD (108). IHD deaths and CVA deaths have been analysed separately, since considering other specific cardiovascular causes of death would have resulted in too small a number of deaths for the groups to warrant a valid statistical analysis.

During a mean follow-up of 11.6 years, 1,632 (968 male and 664 female) deaths occurred among which 794

(48.6%) (505 male and 289 female) were of cardiovascular origin among which 518 (31.7%) (350 male and 168 female) were due to IHD and 159 (9.7%) (79 male and 80 female) were caused by CVA.

4.6.METHODOLOGICAL APPROACH TO FOLLOW-UP STUDY OF SURVIVORS

In order to study the association between asymptomatic hyperglycaemia and later development of overt diabetes a follow-up study of survivors has been arranged. A follow-up survey in October 1987 to April 1988 located about 15% of alive non-diabetics of the Paisley sample. The detailed method of this follow-up is described in section 5 of Chapter 12.

In summary, the CHI holds the patient's name, address, date of birth, gender, marital status, GP's name and address, date of registration with the practice, date of removal, NHS number and CHI number. This information may be matched with that held on a separate Midspan file to determine the last known address of patients as well as the identity of the patient's GP. The practice records could then be examined to collect the required clinical information.

4.7.DEFINITIONS AND STATISTICAL ANALYSIS

4.7.1.Person-Years of Observation

Person-years of observation (PYO) were calculated in order to fully utilize the period of observation for each individual and properly weigh their contribution to the study. PYO refers to the length of time the subject entered the cohort until observation (follow-up) was

terminated. For mortality, observation was terminated at first January 1986 or at death if this occurred previously. For analysis of survivors in Chapter 13, observation was terminated at first April 1988 or at diabetes diagnosis if this had occurred previously. The period of observation was calculated by computer to the nearest day.

4.7.2.Risk and Mortality

Risk and mortality rate are used interchangeably. Rates were calculated for the total and for various subgroups classified by age and gender from the formula: number of mortality events or progressed to diabetes/number of person-years at risk. Where data are not presented for specific age groups, then use was made of standardization to take into account differences in the age composition of subgroups and to remove statistically that portion of any difference attributable to age differentials. The mortality rates were adjusted for age in both genders by the direct method using the 1981 Scottish population as standard. Age adjustment was based on four 5-year age categories: 45-49, 50-54, 55-59, 60-64. The age group 45-49 includes subjects who have just passed 45 and just reached 50. For simplicity, this terminology is also employed here for actuarial type analyses where the equivalent actuarial label would be 45-50 for the same age span.

4.7.3.Cut-off Values

There is no natural limit between normal and an abnormal risk factor level. The risk of CVD increases as the level of any risk factor increases.

The concept of "normal" and the specification for separating "positives" from "negatives" deserves some discussion. The term "normal" can refer to the usual or, typical, values of a characteristic for a population group. It can also be used to describe "functional status" either present or future. In this sense any value can be considered normal if no increased risk has been found to be associated with it. Since the goal of screening is to identify persons who have a disease or are at increased risk for the future, screening is concerned ultimately with a functional definition of normality. However, we must also consider how the statistical use of the term "normal" relates to the goal of screening.

In the present investigation for compatibility with the other studies, the statistical concept of normality was considered. Two standard deviations above and below the mean correspond to the central 95% area under the curve for normally distributed variables. By extension, the normal range in laboratory tests or physiological measures is defined in terms of the central 95% of values derived from a series of presumably healthy individuals. However some biochemical measures are not normally distributed and ranges corresponding to the mean $\pm$ 2SD do not then represent the middle 95% of values. But beyond this, a dichotomous classification of people as "normal" or "abnormal" with respect to a certain value often over-simplifies a complex situation.

In response to problems of this nature Elvebak (137) has suggested that laboratory data on individuals be

presented in terms of a percentile level, and furthermore, that this be specific for age and gender. Such specificity is needed because the same level of cholesterol might represent one percentile value for a 60-year old female, another for a 30-year old male. The use of age-specific percentiles rather than the 95% central range would emphasize that 1) no assumptions are made that the distribution is normal; 2) the same biochemical value e.g. 300 mg/dl of cholesterol, could represent a common value for an older woman, but a distinctly unusual one for a young man and 3) health and disease lie along a continuum and that separation of the two on the basis of a single "cut-off" point may be arbitrary.

In these analyses, comparison of risk by level of the various risk factors, where the risk factor was continuously distributed (as in the case of blood pressure, serum cholesterol, blood sugar and BMI), was usually done by dividing the groups into quintiles. For example, fifths, from the lowest to the highest, and/or upper and lower 5% and 2% of distribution or arbitrary categories established by prior research. The age-specific and age-adjusted mortality rates were computed for the quintiles, upper and lower 5% and 2% or arbitrary categories. Where there were ties at the boundaries of quintiles, individual values were not assigned to the higher or lower quintile so the numbers in each quintile may not be exactly equal.

Comparison was made of the ratios between rates, e.g. for the highest and lowest quintile groups in the term of relative risk.

4.7.4.Standardised Normal Deviate

This statistical procedure was applied in Chapters 10 and 11 concerning the assessement of the comparative strength of various components of blood pressure as predictors of IHD and stroke mortality. As SBP and DBP and derived combinations of them differ in range and variance and also depend upon age and gender, they were transformed to give an age-gender adjusted standardised normal deviate (SND) for each individual by subtracting the age-gender specific mean and dividing by the age-gender specific standard deviation as in the Whitehall Study (120). For example, for a male in the 45-49 age group

$$\text{SND for SBP} = \frac{\text{observed SBP - mean SBP for males in 45-49 age group}}{\text{standard deviation of SBP for males in 45-49 age group}}$$

The SND indicates the degree to which an individual's pressure (whether SBP, DBP, MAP, MAI or PP) deviates from an age specific mean in standard deviation units. These differences provide a direct method for comparing the power of these five measures of blood pressure to discriminate IHD or stroke mortality. The sign gives the direction of the association and the size of the value the strength of the association. If the null hypothesis of no difference between the relative rises in SBP and DBP and derived combinations of them in subjects dying of stroke or IHD is true, we would expect the average difference in those subjects to be close to zero. Significance was assessed by a paired t-test for the difference between

each component of blood pressure and DBP and a two sample t-test for the difference between blood pressure in persons who died compared to subjects who were still alive at 10-14 years.

4.7.5.Logistic Regression Analysis

To examine the contributions of each risk factor as well as calculating adjusted estimates of relative risk as the standardized odds ratio (SOR) to mortality outcome, MLR analysis (BMDP program PLR (138)) was used to allow for confounding factors (139).

The logistic in its univariate form,

$$P=1/[1+\exp(- a - bX)]$$

was also used to provide estimates of risk of a new mortality event over the years of follow-up for men and women separately. Logistic analyses were carried out for individual risk factors (univariate logistic), and adjusted for age (bivariate logistic), and combinations of risk factors (multivariate logistic). They permitted a test of the relationship between continuous variables and all causes, CVD, IHD, and stroke causes of death on a continuous scale. In these logistic analyses, both the logistic coefficient and standardised logistic coefficient were computed. The latter, the product of the logistic coefficient times the standard deviation of the risk variable, served as a measure of the gradient of risk independent of the absolute value of the variable. In multivariate logistic analyses, the standard logistic coefficient permits a comparison of the relative contribution of each independent variable to risk of mortality. SBP, DBP, and the derived MAP, MAI and PP,

age, BMI, serum cholesterol and casual blood glucose were entered as continuous independent variables.

Current cigarette smoking habits were entered as a dichotomous variable (current cigarette smokers and non-smokers).

It was assumed that the probability of dying was

$$1/(1+\text{Exp}[-(a + \Sigma bi\ Xi)])$$

where Xi includes SBP and DBP (mmHg), and the derived MAP, MAI and PP, age in year, gender, BMI (Kg/m^2), blood glucose (mg/dl), serum cholesterol (mg/dl) and cigarette smoking at the initial examination. The parameters of the model (a and b) were estimated using the maximum likelihood method described by Walker and Duncan (139) and the coefficients divided by their estimated standard errors as a test of significance to indicate whether these relationships were significantly different from zero ($P<0.05$ when $Z\geq 1.96$). The numbers of deaths or cases developing diabetes were used as the dependent variables and analysed for males and females separately. To test for differences between the effects of the high and low risk factors, interaction terms comprising one of the blood pressure variables (SBP, DBP, MAP, MAI, PP), blood sugar, BMI and each of the risk factors were included in MLR models. The regression coefficient, b ,affords a measure of the association between increased risk of the event and levels of the characteristics.

The measure used for comparison of the predictive strength of each controlling measure is the SOR. This estimates the (approximate) relative risk (odds ratio) per

unit change in the level of risk factor, Xi, is e^{bi}. More generally, e^{Dbi} approximates the relative risk per D units of change in the level of risk factor (Xi) and can be used to determine the relative risk from the highest to the lowest category of a variable. Because of differences in the usual range of values for confounding variables and since the magnitude of the coefficients is affected by the variance of the characteristic, a direct comparison of the logistic function coefficients is not appropriate to determine the relative predictive strength of each variable. In order to put all the coefficients on the same scale, the coefficient is multiplied by the standard deviation of the variable, and then exponentiated. This gives the odds ratio associated with a change of one standard deviation in the continuous variables of interest. The standard deviations for the distributions of risk factor scores have not been given but they can be computed from information that is provided. The standard deviation equals the ln(SOR) divided by the logistic coefficient.

Statistical significance of the findings was assessed by a variety of methods. Although the tests varied, all were interpreted in a common fashion, i.e. differences, ratios, and other statistics were termed significant if the test indicated that chance alone would account for variation from a value suggested by a null hypothesis with probability <0.05.

In the Tables in the following chapters, certain conventions were used. Where there are no events, the symbol used is -. Statistical significance is indicated

conventionally by a single asterisk for $P<0.05$, a double asterisk for $P<0.01$, a triple asterisk for $P<0.001$. The relevant definitions and statistical methods used in each table are also given in the table's footnote.

CHAPTER 5

BASELINE CARDIOVASCULAR RISK FACTORS AND MORTALITY PATTERN IN RENFREW AND PAISLEY

SUMMARY: This chapter considers the prevalence of baseline characteristics and a brief description of baseline findings in the target community. The prevalence of cardiovascular risk factors at baseline was relatively high. This section also considers, by univariate, bivariate and multivariate analysis, the relation of certain key characteristics to the four causes of death - all causes, CVD, IHD and stroke. These key characteristics -SBP, DBP, serum cholesterol, casual blood glucose and BMI- have been related to at least one of these four causes of death. In general, the relationship appears to be stronger for women than men.

Contents

5.1. INTRODUCTION

This chapter describes the prevalence of baseline characteristics and a brief description of the baseline findings in the target community. This chapter will also consider the evaluation of the role of chosen risk factors in mortality among the baseline survey sample who were followed-up through record linkage with the Registrar General.

The four "causes" of death considered were -all causes, CVD, IHD and stroke- in relation to certain characteristics measured at baseline. The main characteristics considered are SBP, DBP, serum cholesterol, cigarette smoking, casual blood glucose and BMI.

5.2. PREVALENCE OF PRIMARY CVD RISK FACTORS

5.2.1. Smoking

The baseline survey participants were divided into three cigarette smoking categories: current smokers, who smoked regularly more than 5 cigarette each day at the time of examination; ex-smokers, who had smoked regularly more than 5 cigarettes a day, but had stopped; never-smokers, who had never smoked regularly more than 5 a day.

Fifty one percent of men and 42% of women in the area and aged 45-64 years were current cigarette smokers in baseline examination. The proportion of never-smokers increased among women towards the older age groups. However the proportion of both male and female current smokers was lower in older age groups (Table 5.1). This

decrease was more prominent in women than men.

A few of the men (2%) smoked pipes or cigars. The mean daily cigarette consumption among smoking men was 20.5 (SD=8.4) and 16.2 (SD=6.1) among smoking women. The average daily cigarette consumption among the smokers was significantly lower in older age groups in both genders ($F=14.2$, $P<0.001$ for male and $F=15.7$, $P<0.001$ for females). Heavy cigarette smoking (25 or more per day) was observed in 18.6% of men and 5.2% of women cigarette smokers.

5.2.2. Serum Cholesterol

The serum cholesterol levels among the Renfrew and Paisley population (aged 45-64 years) were high; men generally had lower values than women, the average value was 225.6 (SD=40.4) mg/dl for men and 246.7 (SD=47.4) mg/dl for women. The mean values increased from the youngest to the oldest age group among women, but no increase was found among men (Figure 5.1). The distribution of serum cholesterol values by age and gender are presented in Table 5.2. Only 24.4% of men and 12.3% of women had a cholesterol value below 200 mg/dl, while 3.2% and 10.7% respectively had a value over 300 mg/dl. Seventeen percent of men and 20.5% of the women had a serum cholesterol value greater than 260 mg/dl.

5.2.3. Blood Glucose

The average blood glucose value was 93.1 (SD=26.6) mg/dl for men and 91.6 (SD=25.2) mg/dl for women. The mean values increase with advancing age in both genders. In all age groups except age 60-64 men had slightly higher mean blood glucose value than women (Figure 5.2). The

distribution of blood sugar values by age and gender are presented in Table 5.3. Only 0.7% of men and women have a value over 200 mg/dl.

In the estimation of the prevalence of asymptomatic hyperglycaemia the arbitrary criterion of $\geq$126 mg/dl (upper 5% of glucose distribution) was used. The proportion of asymptomatic hyperglycaemic men and women increased towards older age groups. This increase was considerable and almost linear among women, while less marked and even less consistent among men. The proportion of people with asymptomatic hyperglycaemia under 55 years was greater among men than women but the situation was reversed among older age groups (Figure 5.3).

52.4. Blood Pressure

Average blood pressures were also high: the mean values in Renfrew and Paisley were 148.5/86.0 (SD=23.0/13.2) mmHg among men and 150.1/85.1 (SD=25.4/13.5) mmHg among women. The SBP level was higher in the older than in younger age-groups among both men and women. Men under 50 had a mean SBP level higher than women, but in the older age groups women had higher means than men. The mean DBP level was higher in men under 60 years of age but after that women had higher means. However, this varied less by age and gender than SBP. The patterns are presented in Figure 5.4. The distribution of SBP and DBP in Renfrew and Paisley at baseline by age and gender are given in Tables 5.4 and 5.5.

Twenty six percent of men and 30% of women in Renfrew and Paisley had a SBP of 160 mmHg or more and 21.6% of men

and 20.2% of women had a DBP of 95 mmHg or more.

In estimation of the hypertension prevalence rate the arbitrary criteria of ≥160 mmHg SBP and/or 95 mmHg DBP suggested by World Health Organisation (WHO) were used. The proportion of hypertensive men and women increased towards older age groups. This increase was considerable and almost linear among both men and women. Thus whereas the proportions of hypertensives under 50-55 years of age were greater among men than among women, the situation was reversed among the older age groups (Figure 5.5).

Table 5.6 shows the Pearson correlation coefficients between baseline continuous variables.

Pearson correlation coefficients were used to describe the relationship between elevated blood pressures and age, serum cholesterol, blood glucose and BMI. SBP had a positive correlation with age, DBP, BMI, serum cholesterol, and blood glucose in both genders. DBP also had a positive correlation with BMI, blood glucose and serum cholesterol. The correlation between DBP and age was not statistically significant in men. SBP and DBP had the greatest numerical correlation in both genders as expected (0.66). After that, BMI and age had the greatest numerical correlation with SBP (0.20 and 0.20 for male and 0.29 and 0.28 for females respectively) and BMI had greatest numerical correlation with DBP (0.30 for men and 0.35 for women respectively). When men and women were analysed separately, age and BMI explained more of the variation in SBP and DBP among women than among men.

5.2.5. Body Mass Index

The average BMI values in Renfrew and Paisley were

25.7 (SD=3.4) Kg/m^2 for men and 25.6 (SD=4.4) Kg/m^2 for women. The mean value slightly increased from youngest to the oldest age group among women, but no increase was found among men (Figure 5.6). Men under 55 years had a slightly higher mean BMI than women, but in older age groups women had a slightly higher mean than men. The distribution of BMI by age and gender is presented in Table 5.7. Twenty percent of men and 28% of women had a BMI value below 23 Kg/m^2 while 35% of men and 33% of women had a BMI of 27 Kg/m^2 or more.

To estimate the prevalence of obesity an arbitrary criterion of ≥ 27 Kg/m^2 was used. The proportion of obese women increased in the older age groups but this was not true for men (Table 5.7). The Pearson correlation coefficients (Table 5.6) show a significant positive correlation between BMI and SBP and DBP, serum cholesterol and blood glucose in both genders and a significant positive correlation between BMI and age in women.

5.3. BASELINE SURVEY MORTALITY FOLLOW-UP

The 10-14 year risk of death from all causes, CVD, IHD and stroke was studied in the baseline survey sample of both Renfrew and Paisley areas. Univariate, bivariate and multivariate logistic coefficients and SOR are given in Tables 5.8-5.10.

5.3.1. Univariate and Bivariate Analysis

The crude and age-adjusted relationship of age, SBP and DBP, blood glucose, serum cholesterol, cigarette smoking habits and BMI to mortality based on univariate and bivariate logistic regression analysis is presented in

Tables 5.8 and 5.9 for men and women respectively. The data confirm that the relationship between the major risk factors and susceptibility to mortality events is a highly significant one.

As expected, age was strongly associated with an increased risk of death in both men and women. SBP and DBP are consistent and powerful contributors to all causes, CVD, IHD and stroke mortality in both genders which SBP is a slightly stronger predictor of all four causes of death than DBP in both men and women except for females. DBP is a more powerful predictor of stroke mortality than SBP. Further detail concerning SBP and DBP as predictors of IHD and stroke mortality is in Chapters 10 and 11.

Cigarette smoking habit also is confirmed as a significant risk factor for all four categories of death independently of age in both genders.

For women, casual blood glucose was related to all causes, CVD, IHD and stroke mortality independent of age. In men, casual blood glucose had a significant age-adjusted relationship with an increasing risk of death from all causes and CVD but the association with IHD and stroke mortality after age-adjustment was of borderline significance ($P<0.1$) while the crude relationship was statistically significant.

Serum cholesterol is revealed to be consistently and strongly related to IHD and all causes of death independently of age in both genders and to CVD in males.

BMI is less strongly and consistently related to risk of CVD and IHD in women and the relationship was not statistically significant for all causes death in both men

and women and stroke death in men. BMI is related negatively to stroke death in women independently of age. Since it has been shown that being overweight and a gain in weight are associated with a worsening of atherogenic traits (e.g. hypertension), the limited role of obesity as a risk factor in middle age remains an enigma needing further investigation.

5.3.2.Multivariate Analysis

When the seven major risk factors 1) age, 2) SBP, 3) DBP, 4) serum cholesterol, 5) casual blood glucose, 6) cigarette use and 7) BMI are considered simultaneously by applying a MLR model, it is further demonstrated that there is a consistent relationship between each of these traits independently (except BMI) and IHD and CVD in at least one gender.

The method of treating the major risk factor as continuous variables has distinct advantages over categorical classification i.e. defining a risk factor by a fixed cut point (e.g. DBP$\geq$95; SBP$\geq$160 mmHg; serum cholesterol$\geq$250 mg/dl; BMI$\geq$27 Kg/m^2). In this later method much information is lost, e.g. a DBP of 74 mmHg is indistinguishable from one of 94. Moreover, when persons have multiple marginal abnormalities (e.g. DBP 92, SBP 155 mmHg, serum cholesterol 244 mg/dl) their risk may be underestimated and overlooked as 'mild' and without significance.

Age: In the MLR analysis of death age was entered as a continuous independent variable for complete age-adjustment. Age appears as the most important risk factor

among men and women for all causes of death and the risk of death increases with age in both genders.

Cigarette Smoking: In the MLR analysis, cigarette smoking was presented in the form of a dichotomous variable, smokers and non-smokers. In this form of analysis cigarette smoking appears as a pernicious powerful risk factor among men and women for all four death categories.

Blood Pressure: In multivariate analysis, where blood pressure was considered as a control variable or as a contributor to multiple regression, both SBP and DBP were used together. However, when blood pressure is considered by itself it is awkward to use the joint multivariate regression coefficients for SBP and DBP. Hence in Tables 5.8 and 5.9 attention is restricted to the SBP and DBP coefficients which are based on univariate and bivariate analysis but in Table 5.10 the SBP and DBP coefficients which are based on multivariate analysis that include both SBP and DBP components. The effects of single and combined SBP and DBP on multiple regression coefficients will be discussed in detail in Chapters 10 and 11.

In the balance, after age and smoking, SBP appears to be the strongest of the factors considered for all causes and IHD in both genders, while DBP appears to be strongest of the considered factors for stroke and CVD in both genders. The relationship between DBP and stroke mortality is particularly strong. SBP was a significant predictor in both men and women who died from all causes, CVD, IHD and males who died from stroke. DBP was a significant predictor in both men and women who died from CVD and

stroke and in males who died from all causes and IHD.

Serum Cholesterol: Serum cholesterol was another significant predictor only in men and women who died from IHD and men who died from CVD.

Blood Sugar: A standardized glucose tolerance test was not administered in this study, so assessment of "asymptomatic hyperglycaemia " is less than optimal; but as may be judged from data in univariate, bivariate and multivariate analyses, casual blood glucose bears a distinct relationship to mortality from all causes and CVD for both men and women and IHD and stroke mortality in females. However, the relationship of casual blood glucose to IHD and stroke mortality events appears to vary with gender. Further detail regarding gender differential in the relationship between high casual blood glucose and mortality will be discussed in Chapter 7.

Body Mass Index: BMI had a negative association with female overall causes of deaths and females who died from stroke.

5.4.GENDER DIFFERENTIAL

In terms of SORs each of these risk factors, except DBP, appears to be more strongly related to IHD in women than in men. In multivariate analysis there is a suggestion that casual blood glucose may not make a contribution independent of age to IHD in men. In fact the relationship between casual blood glucose and IHD is stronger for women than men. In multivariate analysis DBP was not a significant independent predictor of IHD in females. This is due to the inter-relationship between SBP

and DBP. In univariate and age-adjusted logistic regression it was a statistically significant predictor of IHD in both genders.

For stroke mortality the association of cigarette smoking and DBP is stronger in females. SBP, on the other hand, had a stronger relationship in men. There is a suggestion in MLR analysis that casual blood sugar positively and BMI negatively are related to stroke in women but not in men.

The relationship of CVD to blood pressure is stronger in men, while cigarette smoking, casual blood glucose value and age have a stronger relationship to CVD in women.

The association between all causes of death and cigarette smoking, age, and DBP is stronger in men. SBP, and casual blood glucose, on the other hand, had a stronger relationship to all causes mortality in women. The gender differential in mortality will be discussed in more detail in Chapter 9.

5.5.MISSING VALUES

One of the major limitations of these data is the large number of missing values for blood glucose. There are 4,613 (30.3%) cases which are missing. In the first three sectors of Paisley town the blood glucose was not measured. In Renfrew this problem did not exist.

Table 5.11 compares the cardiovascular risk factor and age-adjusted mortality rate between blood glucose missing and study groups. As shown in Table 5.11 the 10-14 years all causes, CVD and IHD mortality rate is slightly higher in both genders and stroke in males in the blood glucose missing group compared to the study group. This

difference is statistically significant (Mantel-Haenszel chi-square) only in males who died from all causes, CVD and males and females who died from IHD. Table 5.11 also shows the mean levels of various possible CVD risk factors in two groups. The study group was slightly older than the group with missing blood glucose. Mean SBP and DBP and mean BMI and proportion of cigarette smokers are slightly but significantly increased in the group with missing blood glucose in males and females but the mean serum cholesterol level was significantly higher in the study group. The 95% confidence interval (CI) shows that the magnitude of differences is not large.

5.6. LATER MORTALITY

The mortality rate in the Renfrew and Paisley study population was unexpectedly lower than that for the general population (Tables 5.12 and 5.13).

Originally this low mortality represented the effect of selection. Whereas it was lower in the respondent part of the sample, it was correspondingly higher in the non-respondent part. This initial difference between respondent and non-respondent mortality can reasonably be explained by the presumption that persons who were seriously ill were less likely to appear for examination than persons who were well. However, among the persons who gave no reason for not appearing for examination, or simply declined to come in, there must also have been some who were seriously ill, for this group also had an excess mortality at the beginning of follow-up period.

In Renfrew, sixteen people who had died between the

time of the census in 1971 and primary screening were excluded, as were 152 who were in hospital, ill at home, or moved from the district. The situation for Paisley remains unknown.

If the lower mortality rates observed in respondents can be explained by high mortality in non-respondents an estimation of the excess mortality in this group can be calculated using national figures. The excess mortality for the non-respondent sample that represent indirectly through national base mortality was quite large for the years 1972 and 1974-76. This was a period when the first examination cycle was still in progress -a period, that is, when it was difficult to specify whether a person did not come in because he had already died or did not come in and then died. By 1976, however, the initial examination cycle was essentially completed; that is, the non-respondent group consisting of people who were alive was defined without ambiguity. Excess mortality in the non-respondent sample remained great through 1972 and 1974-1976.

In 1977, however, mortality slightly increased in the study population but was still less than that for the national population as a whole and remained at that level. Thus, in the non-respondent group, selection bias seems to have become a minor influence by 1977.

The issue, however, is clouded by questions about the completeness of mortality follow-up. When a 15% sample of the study population was matched with names on the CHI (the procedure is described in Chapter 12) we found about 8.5% of the mortality reported to CHI from 1977 to 1986

was not in the Renfrew and Paisley data file. If the situation was the same and no worse for the years 1972 to 1976 more missing mortality is expected. Some people were transferred from Argyll and Clyde Health Board's CHI and so, the mortality of this group has not been examined in this study. Thus, the completeness of mortality follow-up, through "flagging" with NHSCR, is under question and recommended for further investigation. However, this mortality report is supported by Isles et al. (140), in an independent but more limited study of Renfrew and Paisley data, who found about 5% shortfall in the flagging system.

CHAPTER 6

ASSOCIATION BETWEEN ASYMPTOMATIC HYPERGLYCAEMIA AND RISK OF CARDIOVASCULAR AND ALL CAUSES MORTALITY

SUMMARY: A possible association between asymptomatic hyperglycaemia and mortality during the subsequent mean follow-up of 11.6 years (range 10-14 years) has been investigated among 10410 men and women aged 45-64 in the west of Scotland. When quintiles of casual blood glucose distribution were considered, no trend of age-gender adjusted mortality rates was apparent. However, for individuals with blood glucose above the 95th centile there was a significantly higher mortality rate compared to the lowest 5 percent, excluding known diabetics. Multivariate analysis, taking into account age, gender, blood pressure, serum cholesterol, BMI and cigarette smoking showed the positive association between initial casual blood glucose level and subsequent mortality. Age, blood pressure, cigarette smoking and gender were also significant predictors of subsequent age-gender adjusted mortality rates. The data support the hypothesis that asymptomatic hyperglycaemia defined as the upper 5% of casual blood glucose distribution was a significant risk factor for mortality in this population aged 45-64.

CONTENTS

CHAPTER 6

6.1. INTRODUCTION

An increased macrovascular disease mortality (coronary, cerebral, aortic and peripheral) in diabetics has been shown in several studies (141-147). But the association of apparently asymptomatic hyperglycaemia to mortality caused by cardiovascular disease still remains controversial. It is currently unclear as to whether hyperglycaemia increases IHD mortality except among those with extremely high postchallenge hyperglycaemia. Nevertheless, the relationship of asymptomatic hyperglycaemia to other forms of occlusive vascular disease such as stroke remains unclear. The analysis of eleven prospective studies by the International Collaborative Group (148) reveals no consistent relationship between asymptomatic hyperglycaemia and IHD mortality. However, some studies have shown an increased IHD mortality rate at the upper extreme of the blood sugar distribution (31). On the other hand, persons with IHD have a higher prevalence of hyperglycaemia than members of the general population of similar age and gender (29, 30). In addition, apparently healthy persons with impaired glucose tolerance have higher level of a number of suspected coronary risk factors than subjects with normal glucose tolerance, and differences are partially independent of age and adiposity (150-152).

These diverse observations suggest a relationship between blood glucose level and development of IHD that is non-linear, complex, and possibly mediated through other physiological variables.

In summary, concern with determining whether asymptomatic hyperglycaemia is, in fact, a cardiovascular risk factor, has been stimulated by at least three sets of observations. First, while in most countries, an excess of atherosclerotic complications and higher cardiovascular mortality rates have been reported for persons with symptomatic diabetes, there is evidence that this is not true world-wide; for example, in some non-"Western" countries with less atherosclerosis (144, 146, 153-155). Second, in animal experimental work, although it was possible to produce both hyperglycaemia and clinical diabetes, this was not accompanied by an intensification of atherogenesis (155). Third, evidence is scant to support the view that because clinical diabetes has been commonly (although not universally) associated with excess atherosclerotic morbidity and mortality, it therefore follows that this is also true of asymptomatic hyperglycaemia.

One means of elucidating this important unsolved question is through epidemiological investigation, in large population groups, of possible associations of asymptomatic hyperglycaemia with an excess of IHD, CVD and stroke morbidity and mortality.

Hawthorne and Gilmour (44) found no association between asymptomatic hyperglycaemia and coronary mortality after 6 years in 1,134 men screened in the Burgh of Renfrew, Scotland. This study as well as most of the other International Collaborative Studies was based on relatively few mortality data and years of observation. Mortality follow-up, in particular, requires either large

numbers or many years of observation if meaningful comparisons are to be made. However, caution is required in drawing conclusions.

This chapter is concerned with the association between casual blood glucose concentration and subsequent 10 to 14 years CVD globally and IHD and CVA separately and overall mortality in 10,410 men and women in Burghs of Renfrew and Paisley age 45-64 in the west of Scotland. In this report it is postulated that hyperglycaemia and interaction of high blood glucose level with other factors increases the risk of cardiovascular mortality especially IHD mortality in the general population.

In addition, the relationship between factors measured at baseline and subsequent mortality from IHD, CVD, stroke and all causes in the asymptomatic hyperglycaemics have been re-analysed.

6.2. ANALYSIS

To evaluate the relationship of casual blood glucose levels at baseline to 10-14 years mortality, univariate quintile analyses were carried out. Bivariate analyses were also done; continuous variables were dichotomized at arbitrary cut points that could be considered "high" and also the men and women classified by smoking habits at entry. For glucose, the cut point divides the upper 5% of the baseline glucose distribution from the remaining 95%. The statistical significance of differences in rates by glucose quintiles in univariate and bivariate analysis were tested by chi-square or F-test. The chi-square test

procedures described by Mantel and Haenszel (156) was applied for statistical comparisons of the rates in the four 5 year age group.

6.3.RESULTS

6.3.1.Baseline Characteristics

In addition to analyses of the possible association between asymptomatic hyperglycaemia at baseline and follow-up mortality, data on those with and without known diabetes were examined. Table 6.1 displays the data for those with diabetes and those without diabetes at baseline. Only 39 (men 15, women 24) of 126 known diabetics died during the mean follow-up of 11.6 years. Age, gender adjusted death rates for all cardiovascular and coronary causes are higher among the 126 individuals (men 62, women 64) known as diabetic than among the 10,410 (men 4,696, women 5,714) non-diabetics in this univariate analysis. This difference was considerably higher in female diabetics than males. Also, age-adjusted death rates for all causes and cerebrovascular causes are considerably higher in female diabetics but not male diabetic subjects. These differences were statistically significant only for female all causes, CVD, IHD and stroke mortality (Mantel-Haenszel chi-square, df=1, $P<0.001$). Female known diabetic subjects experienced all causes, all cardiovascular, coronary and cerebrovascular age-adjusted death rates 3.5, 5.1, 4.7 and 10.8 times higher than those without diabetes respectively. The figures for known male diabetics were 1.0, 1.2, 1.5 and 0.8 respectively. The number of cerebrovascular death was relatively small and caution must be taken in the

interpretation of the results. The greater mortality of men relative to women for non-diabetic and the greater mortality of women relative to men for diabetics are observed in all four mortality groups. The small number of cases does not allow further conclusions.

Known diabetics at baseline are omitted from the remaining analysis of mortality and the final study population by age and gender is shown in Table 4.2. The distribution of casual blood glucose in the total population of men and women aged 45-64 year is shown in Figure 6.1 and is skewed to the right. Those 498 (280 men and 218 women) subjects at the extreme upper 5% of blood glucose, with blood glucose in the range of 126 mg/dl and above have been called "asymptomatic hyperglycaemics". The prevalence rate of asymptomatic hyperglycaemia was 6% for males and 3.8% for females. This difference is statistically significant (X^2 =26.6, df=1, P<0.001) and increases with age in both genders.

Table 6.2 presents means, standard deviations, and ranges of major variables measured at baseline for the 10,410 (4,696 men and 5,714 women) individuals age 45-64. Simple correlation coefficients (non-parametric) of these variables with casual blood glucose are also shown, with age, SBP, DBP and BMI showing positive significant correlations as expected, and with serum cholesterol showing a negative significant correlation in both genders. Although these correlations were statistically significant, they were of low order except with SBP.

As indicated in Table 6.3, the level of blood sugar increased steadily with advancing age, and the linearity is statistically significant in both genders, and males have a higher level of blood glucose than females in all age groups. This finding is compatible with other studies (157-161).

The smoking status at baseline is shown in Table 6.4. About 45% (male 49% and female 41%) of subjects smoked 5 or more cigarettes per day, with 80% of these smoking 10 to 20 cigarettes daily. Table 6.4 also displays the mean glucose values for the smoking strata. The mean casual blood glucose value was higher in never smokers and ex-smokers than current smokers. Although these differences were statistically significant, they are small (male, $F=7.7$ $P<0.0005$; female , $F=9.9$ $P<0.0001$).

Table 6.5 displays the age, gender adjusted prevalence rates for different smoking classes by quintile and top and bottom 5% and 2% of casual blood glucose. The prevalence of smokers decreased (male $X^2=20.4$, $P<0.01$, female $X^2=26.3$, $P<0.0001$) and the prevalence of never smokers increased with the glucose level (male $X^2=11.4$, $P<0.05$, female $X^2=19.6$, $P<0.001$) in this material. There was an excess of current smokers in the lowest quintile of casual blood glucose (male $X^2=12.2$, $P<0.01$, female $X^2=21.8$ $P<0.01$, bottom quintile compared with the corresponding upper quintile). In the lowest 5% compared to highest 5% again these differences exist but in lowest 2% compared to top 2% the difference was not significant, probably due to small numbers of individual in these percentiles. Also, when age adjustment was made by summing up the chi-square

analyses in four 5 year age groups, there appeared to be significant correlation between smoking prevalence and blood glucose quintile.

6.3.2.Ten to Fourteen Year Mortality Data

Table 6.6 shows the results of univariate quintile and extreme values analyses in relation to 10 to 14 years age-adjusted mortality rates for all causes, CVD, IHD and stroke. A non-linear relationship was found between blood glucose levels and the 10 to 14 years mortality from all causes, CVD, stroke and IHD. There was a doubling of IHD mortality rate at the top 5% compare to the bottom 5%. The mortality rates in the top 5% or 2% of blood glucose were significantly higher than the corresponding mortality rates in the lower 5% or 2% for female overall causes males and females IHD and CVD. After age adjustment, for male, the Mantel-Haenszel chi square test revealed that only for CVD and IHD did the data indicate that the highest 5% and 2% of sugar distribution had a significantly higher death rate than the corresponding lowest 5% and 2% (for all causes of death the highest 2% of sugar distribution was of borderline significance, $P<0.1$); for female it was significant for CVD and all causes for the upper 2% of glucose distribution, but for the highest quintile it was not significant. For stroke none of the upper extreme values were significant. However, the number of stroke mortality events was not large, so that rates using this cross classification method must be recognized as unstable. The major variables are dichotomized at arbitrary cut-points that

could be considered "high". For glucose, the cut-point divides the upper 5% of the baseline glucose distribution from the remaining 95%.

Table 6.7 present further univariate analysis. The relative risk of IHD, CVD and all causes death for those "high" on such variables as blood glucose, SBP, DBP and serum cholesterol is considered. When the top 5% of blood glucose distribution is considered, those with blood glucose 126 mg/dl or greater had a relative risk of coronary death of 1.47 for males and 1.69 for females compared with those with under 126 mg/dl. Also, to a lesser extent the relative risk for CVD and overall causes mortality was higher in males and females. There is thus evidence for a non-linear relationship between blood glucose and IHD as well as CVD and overall death, with a significant increase in mortality occurring at the higher extreme of the blood glucose distribution.

6.3.3.All Causes CVD, IHD and Stroke Mortality by Other Risk Factors

Bivariate analyses were carried out to examine the effect of SBP, DBP, serum cholesterol, BMI or smoking habits on the relationship between blood sugar levels and mortality. In Tables 6.8, 6.9, 6.10, 6.11 age adjusted overall causes, CVD, IHD and stroke mortality rates are given for the normoglycaemic and asymptomatic hyperglycaemic groups according to possible CVD risk factors. Mortality from all causes, CVD and IHD was higher in the top 5% of blood glucose irrespective of the level of SBP, DBP, serum cholesterol, BMI or smoking habits. For male stroke mortality it is not consistent due to very

small numbers of deaths in hyperglycaemic group during the follow-up period. For continuous variables - cholesterol, SBP, DBP, BMI- and the categorical variable -smoking- mortality rates are given for subjects above and below the selected cut-off points-i.e. 250 mg/dl for cholesterol, 160 mmHg for SBP, 95 mmHg for DBP, 27 kg/m^2 for BMI. For overall causes of death current cigarette smoking in both genders and high DBP in females do not confer as high a relative risk of all death in the asymptomatic hyperglycaemic group as in the normoglycaemic one. For CVD, high SBP and cigarette smoking in both genders and high DBP in male and high cholesterol in females do not confer as high a relative risk of CVD death in the asymptomatic hyperglycaemic groups in the normoglycaemic one. For IHD, a high SBP and DBP and current cigarette smoking in males and females do not confer as high a relative risk of IHD mortality in asymptomatic hyperglycaemic group as in the normoglycaemic one. For stroke, a high cholesterol and SBP for male and current cigarette smoking in female do not confer as high a relative risk of stroke death in the asymptomatic hyperglycaemic group as in the normoglycaemic one. However, for high BMI in both genders, the relative risk of CVD, stroke and overall death is greater in the asymptomatic hyperglycaemic group. For high BMI in females, the relative risk of IHD death is greater in the asymptomatic hyperglycaemic group. For high cholesterol in both genders, the relative risk of overall, IHD and stroke mortality is greater in the asymptomatic hyperglycaemic

group. For high cholesterol in males, the relative risk of CVD mortality is greater in the asymptomatic hyperglycaemic group. For high SBP in both genders, the relative risk of overall death is greater in the asymptomatic hyperglycaemic group. For high SBP in female, the relative risk of stroke death is greater in the asymptomatic hyperglycaemic group. For high DBP in both genders, the relative risk of stroke mortality is greater in the asymptomatic hyperglycaemic group. For high DBP in males, the relative risk of overall death is greater in asymptomatic hyperglycaemic group. For high DBP in females, the relative risk of CVD mortality is greater in asymptomatic hyperglycaemic group. Comparison of relative risk of hyperglycaemic and normoglycaemic groups in this bivariate analysis suggests the presence of interaction between glucose and other variables. To remove this interaction effect multivariate logistic regression with interaction terms between glucose and the rest of variables has been done.

As shown in Table 6.12, the 10-14 year IHD, CVD and overall causes mortality rate is increased above the 95th centile of blood sugar, for both genders. Deaths from CVD accounted for 63.1 (male 58.7, female 70.0) percent of all deaths in asymptomatic hyperglycaemic group, whereas only 47.4 (male 51.6, female 41.3) percent of all deaths were attributed to this cause in the normoglycaemic group. Table 6.12 also shows the mean levels of various possible CVD risk factors above and below the blood glucose 95th centile cut points. The mean age was significantly higher for women with asymptomatic hyperglycaemia than for

normoglycaemic women. In men age was higher in the asymptomatic hyperglycaemic group than normoglycaemic group, but the difference was not statistically significant. Mean SBP is significantly increased above these limits in males and females and mean BMI is significantly increased in males, but there are no significant differences in mean DBP or lower mean serum cholesterol, or the lower proportion of cigarette smokers in the asymptomatic hyperglycaemic group (Table 6.12).

6.3.4.Multiple Logistic Analysis

The univariate and bivariate findings clearly indicate that the role of asymptomatic hyperglycaemia as a risk factor for death can be properly evaluated only by taking account of the confounding effects of other risk factors. Therefore, the independent contribution of blood glucose level to the risk of 10-14 year mortality was assessed by a series of multivariate logistic analyses. The mean and standard deviation of the variables for persons who died from overall causes, CVD, IHD or stroke are compared to those who live (Table 6.13). Persons who died from IHD and CVD had higher mean levels of all variables measured at baseline than those who survived. Individuals who died from all causes and stroke had higher mean levels of blood glucose, blood pressure and they were older than those who survived.

The MLR analyses of mortality data (Table 6.13), shows a significant positive contribution of age, gender, SBP, DBP, blood glucose and cigarette smoking and a negative contribution of BMI and serum cholesterol to the

all causes mortality. For IHD, and to a lesser extent, for cardiovascular causes, age, gender, blood pressure, blood glucose, serum cholesterol and cigarette smoking contribute positively to mortality. For cerebrovascular disease, blood glucose, age, DBP and smoking contribute positively and BMI negatively to mortality. In all regression procedures all variables were entered as continuous variables except gender and current smoking habits (yes and no). In the model with interaction terms, there is a significant association between sugar and gender as a predictor variable for all causes, CVD and IHD. From the coefficient from the logistic model for any difference in mortality by age, gender, degree of blood glucose, SBP, DBP, obesity or smoking a ratio can be calculated expressing the relative odds of death in the 10-14 year period. The adjusted odds ratio of all causes, IHD, CVD and stroke mortality has been calculated. This adjusted estimated relative risk of blood glucose for IHD and CVD death is approximately 12% and 14%, for all causes and stroke mortality, 9% and 16% respectively increase with a change by an amount equal to its standard deviation. Several of the possible CVD risk factors are significantly correlated with each other and with blood sugar (36). To assess the independent relationship of each variable with IHD, CVD, stroke and overall death, another MLR analysis has been carried out for the normoglycaemic and asymptomatic hyperglycaemic groups separately (Table 6.14). For the normoglycaemic group gender, age, SBP, DBP, and smoking were significantly related to IHD, CVD, stroke and all causes death. Serum cholesterol was not related to stroke mortality. BMI

was not related to CVD and IHD death. Blood sugar was not a significant predictor of CVD, IHD, overall causes death and stroke mortality in normoglycaemic group. In asymptomatic hyperglycaemic group blood glucose and age were significantly related to IHD, CVD, stroke and overall causes of death. DBP was also significantly related to stroke and CVD mortality and SBP to all causes and IHD deaths. Cigarette smoking also was significantly related to all causes, CVD and IHD mortality. Gender was also significantly related to CVD and IHD mortality

6.4.DISCUSSION

In this chapter, the role of asymptomatic hyperglycaemia as a possible risk factor for CVD, IHD, stroke and overall causes of death has been examined in the middle-aged population of Renfrew and Paisley in the west of Scotland.

Several studies have shown that clinically manifest diabetes mellitus is connected with an increased risk of premature death, especially from CVD, and particularly in diabetic women (141-147). The diabetic men and women in the Renfrew and Paisley survey were also found to have an excess mortality from all causes as well as from CVD and IHD as compared with non-diabetic control subjects. This difference was considerably higher in female diabetics than male. In an earlier report from the Framingham study (162), "diabetes" was a significant independent predictor for IHD in both men and women but in a more recent analysis (163) of a cohort aged 50 years and above, this is true only for the women. Also, the Evan County

prospective population-based study (164) suggests that diabetes predicts heart disease only in women after adjustment for covariates. Findings of this study support the finding of the Framingham Study (165) that diabetic women experience higher cardiovascular mortality than men. The reason for the greater susceptibility of women to these cardiovascular sequelae of diabetes is not clear (141, 166).

In this study, as expected, the casual blood glucose correlated with blood pressure, obesity, and age. The negative relationship of serum cholesterol and blood glucose level was also expected. The inverse correlation of smoking habits and casual blood glucose level was somewhat unexpected. Obesity may be one of the explanatory factors, because it is well established that in population studies smoking habits and obesity tend to be in inverse correlation. Similar results were obtained in the Helsinki Policemen study (42) in 2-hr post load blood glucose and this association was found to persist after controlling for age and BMI. In the Social Insurance Institution's Coronary Heart Disease study smoking showed an inverse relationship to 1-hr post-load blood glucose but this association was found to be almost entirely explained by the opposite trends of smoking prevalence and blood glucose with age (41). In the same analysis we found in the multivariate analysis model using an interaction term that there was a significant inter-relationship between BMI and smoking as a predictor variable for all causes and IHD death.

In the Renfrew and Paisley cohort study, univariate

analyses showed a positive non-linear relationship between blood glucose and the 10 to 14 years mortality from all causes, CVD, IHD and stroke with the top quintile or 5% or 2% showing linear trends. The Whitehall study (43) suggests a threshold of risk rather than a graded or linear relationship as observed here. It is possible that for glycaemia (unlike cholesterol and blood pressure) the relationship to mortality risk, particularly CVD risk, is a threshold rather than a linear or curvilinear one i.e. consistently positive association between the highest level of asymptomatic hyperglycaemia (e.g. the upper 2-5% of distribution) and IHD or CVD. Similarly, in the population based study of Busselton, Australia (167), 12-year CVD mortality for men over 60 years of age was significantly higher (more than double) in men with baseline 1-hour post-load glucose exceeding 200 mg/dl (highest 2.5%) than in those with a glucose level below the mean. On the other hand, there was no significance in mortality when the top quintile of glucose was compared with the lower level. In the International Collaborative Group, they do not consistently show evidence for a threshold relationship. In the present study, men and women with asymptomatic hyperglycaemia (upper 5% of glucose distribution) showed distinctly higher mortality rates than those for men and women in the bottom 95% of blood sugar distribution. Age-adjusted mortality rates from all causes were about 70% higher in the top 2% of casual blood glucose than in the bottom 2%.

On the other hand, the relationship of asymptomatic

hyperglycaemia to CVD morbidity and mortality is more controversial. In two cross-sectional population-based studies from Bedford, England (31) and Tecumseh, Michigan, U.S.A. (30), there was a significant association between hyperglycaemia defined by elevated post load glucose levels and the prevalence of IHD. This association was noted even in the range of borderline or moderate hyperglycaemia, and remained significant when blood pressure (in both studies) as well as serum cholesterol (in Tecumseh) were taken into account. However, in a report from the International Collaborative Group, rather inconsistent results have been shown on the relationship of blood glucose to IHD prevalence as indicated by electrocardiographic abnormalities, and to overall, CVD and IHD mortality. In this project the age-adjusted mortality rate for all causes, CVD and IHD were related to the quintile of baseline blood glucose level. Furthermore, the independent role of blood glucose for the risk of mortality was assessed by MLR analysis taking account of other cardiovascular risk factors such as age, blood pressure, BMI, serum cholesterol and cigarette smoking (36).

In the International Collaborative Group, 11 studies presented mortality data with long-term follow-up, varying from four to 15 years. In univariate analysis, the relative risk for overall mortality, when the top quintile of glucose level was compared with the bottom quintile, was greater than 1.0 in nine studies, although it reached 2.0 or greater only in two studies. For CVD and IHD mortality, the relative risk of approximately 2.0 or

greater was noted in four studies. In multivariate analysis, however, a significant association of the baseline glucose level with subsequent mortality was noted for all causes in three studies, for CVD in two studies and for IHD in only one study. Thus, the results of this collaborative project do not indicate a consistent and strong association between asymptomatic hyperglycaemia and mortality. This is especially true when the confounding effects of other risk factors are taken into account.

Age-adjusted mortality rates in the Renfrew and Paisley middle-aged populations from all cardiovascular disease and from IHD separately were 2.5 times higher in the upper 2% than in the lower 2% of casual blood glucose in both genders and in stroke it was 4 times higher in males and three times higher in females. In a 5-year follow-up study of Whitehall individual with blood glucose above the 98th centile, there was about a doubling of IHD mortality, this increase being independent of age and blood pressure (43). Also, in the 7.5 year follow-up, the upper 5% of the blood glucose distribution was associated with a doubling of IHD mortality, independent of other risk indicies (35). Again, the 10 year mortality data confirm the sharp doubling of risk of IHD above the 95th centile of the blood glucose distribution found in the 7.5 year mortality analysis and this increased risk persisted after adjustment for other associated variables (168). In the Bedford survey, age corrected mortality rates, from all causes and coronary heart disease were higher in "borderline" diabetes but when adjustment was made for

other risk factors the differences were significant only for all death in women (31). Similarly, those with the highest glucose values in Tecumseh exhibited a weak but a statistically significant positive association with IHD mortality (169). Also, in the Paris Prospective Study (7) in univariate analysis the overall death rate was two and half times higher in the upper 2.5% than the mortality rate in the whole group. Also, Yano et al. (170) in their study of nine-year mortality in Japanese men in Hawaii found age-adjusted mortality for death from all causes, CVD, IHD and causes other than CVD and cancer were significantly higher in men with glucose intolerance, defined by either medication for diabetes or 1-hour post load serum glucose level above the 90th percentile cut-point (225 mg/dl) at baseline examination, than in normoglycaemic men. This finding as well is in accord with those in the Chicago Peoples Gas Company Study (39) which was the only group in the International Collaborative Project showing a significant relationship of 1-hour post-load glucose consistently with overall, CVD, and IHD mortality, even after controlling for other risk factors. It is not clear why such inconsistent results have been shown in different studies. However, one of the reasons may be that there is a non-linear relationship between blood glucose and mortality.

Multivariate analyses using the MLR model carried out to determine the impact of asymptomatic hyperglycaemia on all causes, CVD, IHD and stroke mortality, taking other risk factors into account, show an independent positive relationship of blood glucose with IHD, stroke, all

cardiovascular and overall causes of death. As judged by the size of the SOR of all causes, CVD, IHD and stroke mortality on the various risk factors, although blood glucose level is significant, it is of low order. Age, smoking and blood pressure appeared to be significant risk factors for overall, CVD, IHD and stroke mortality, as expected. Also serum cholesterol was a significant risk factor for CVD and IHD death. BMI has not been a risk factor for CVD and IHD whereas it has a negative relationship with stroke and overall mortality in this study. Investigation into the operation of other possible CVD risk factors in the asymptomatic hyperglycaemic group (Table 6.8-6.11) showed that an increased serum cholesterol, SBP and DBP in males, and overweight in both genders, are associated with a higher relative risk of overall mortality than that in normoglycaemic individuals. In CVD, an increased BMI in both genders, and in IHD an increased serum cholesterol in both genders and BMI in females and in stroke an increase of BMI and smoking in males and serum cholesterol and blood pressure and BMI in females than that in the normoglycaemic individuals was found. However in the MLR analysis (Table 6.14), BMI, gender, serum cholesterol, smoking habit and SBP do not appear as significant independent predictors in asymptomatic hyperglycaemia in any of the mortality groups. Only blood glucose and age appear as significant independent predictors in the asymptomatic hyperglycaemic group in all four mortality outcomes. Also DBP was a significant predictor of CVD and stroke mortality. Most of

the International Collaborative Studies found the positive association of blood glucose and subsequent ECG abnormalities. The results of eight of the International Collaborative Group studies were negative or showed a slight association between glucose tolerance and IHD mortality (148), whereas three studies showed a relative risk of two or more for those in the top glucose quintile. In most of the International Collaborative Studies because of insufficient mortality data and a short follow-up period for meaningful statistical analyses, the upper 5 and 2% of glucose values were not calculated. However in multivariate analysis, only one of these three studies showed a significant relationship between glucose level and IHD mortality, when other risk factors had been controlled. In the Helsinki Policemen study (42) only in univariate analyses a positive non-linear relationship between blood glucose and 10-yr mortality from all causes, CVD and IHD was found. Therefore, it is quite possible that this non-linear trend of IHD mortality with blood sugar may not be detectable in prospective studies with smaller overall numbers because a sufficient number of IHD deaths has not occurred in such an extreme range of the blood sugar distribution. This non-linearity probably explains why blood sugar did not appear as a significant predictor of IHD in the MLR analysis of some of the International Collaborative Studies, who found the association in univariate analysis.

If, indeed, asymptomatic hyperglycaemia itself was a risk factor, then perhaps a simple measurement of casual blood glucose might serve to identify individuals with

subclinical atherosclerosis or with increased risk of developing cardiovascular manifestations. The finding of this survey support the encouragement to that view. When known diabetics were excluded, rates of subsequent mortality of major cardiovascular events were significantly higher in this group.

Diabetics could be prone to premature cardiovascular deaths because of a higher prevalence of other risk factors for cardiovascular disease among them. In this study, after excluding diabetics, casual blood glucose was significantly correlated with blood pressure, age, gender, BMI and smoking status. However, it should be noted that survivors in 1986 with low blood sugar value in 1972-1976 had particularly low values of blood pressure, and they were younger, thinner and perhaps non or ex-smokers.

Bivariate analysis of the data shows that blood pressure, use of cigarette, serum cholesterol and casual blood glucose were higher among 45-64 year old men and women who died from cardiovascular disease in the next 10-14 years. These factors were risk factors for death from overall causes as well. Serum cholesterol measured at the age of 45-64 was not found to be a statistically significant risk factor for overall causes of death within a span of about a single decade. In MLR analyses, including baseline casual blood glucose values, blood pressure, smoking habits and serum cholesterol were again found to be independent risk factors for death from CVD, IHD and stroke mortality events. However a word of caution is needed. The problem is whether casual blood glucose is

a sufficiently sensitive measure. These arbitrary criteria are at variance with those for diabetes and impaired glucose tolerance based on fasting blood sugar levels or the standard glucose tolerance test that has been proposed by the National Diabetes Data Group (171) and recommended by the World Health Organization (172). However, in an epidemiological investigation examining a large cohort of people in a community, it is rather difficult to require that all subjects arrive in the fasting state or to require that they remain for 2 hours after glucose challenge, plus it is seldom practical to determine several glucose values from economical point of view. On the other hand, casual and various post-challenge glucose determination yield remarkably similar results in different studies (41, 43, 143, 167).

Diuretics used in antihypertensive therapy may influence the level of glucose. Medication history obtained at baseline did not differentiate between diuretics and other hypotensive drugs. However, a large proportion of hypertensives were on drug treatment, and Hawthorne and Gilmour both included and excluded these groups and found no difference (44). So, hypertensive men and women on drug therapy were not excluded from this study.

Clinical observation has found CVD to be common among diabetics. In addition, retrospective case-control studies have found hyperglycaemia to be more common in those with IHD than in the normal population. These observed associations between blood glucose and CVD are supported by the present prospective study, that individuals with above

threshold blood glucose values have higher incidence of IHD, CVD, stroke and overall causes of death. The prospective findings of this survey support the idea of elevated blood glucose being an independent risk factor.

At the extreme upper 5% range of blood glucose concentration, defined as asymptomatic hyperglycaemia, there were higher levels of mean SBP for males and females and BMI for males (Table 6.11). As has been noted in other studies (31, 173), there was a significant positive correlation between blood glucose and SBP over the whole blood glucose range (174). The proportion of current cigarette smokers was lower for individuals above the 95th centile of blood glucose distribution. This difference was not statistically significant. Thus, this finding does not support the finding of other workers (175, 176) who have suggested that increased cigarette smoking may explain in part the increased arterial disease in diabetics. This finding supports the same results from the Bedford and Whitehall Studies (31, 43).

Asymptomatic hyperglycaemic individuals, in general, have higher level of CVD risk factors than normoglycaemic individuals. Asymptomatic hyperglycaemic men and women in the Paisley and Renfrew cohort study had higher SBP and were more obese. However, they smoked less and had lower serum cholesterol. This finding is compatible with the finding of the Framingham Study in diabetic men (165). Although the higher level of SBP in the asymptomatic hyperglycaemic group might suggest it, the excess risk of cardiovascular sequelae in asymptomatic hyperglycaemia is

not entirely a function of a higher level of SBP. In the present study the association between asymptomatic hyperglycaemia and stroke mortality in men and women was inconsistent. This could be due to small number of stroke deaths at such extreme values. It is recommended that this be re-tested after sufficient mortality data is collected.

In summary, these prospective analyses -univariate, bivariate and multivariate- yield reasonably consistent results indicating an association between glycaemia and coronary, cardiovascular and overall mortality outcome. These findings suggest that this association may depend on gender. Men and women in the upper 5% and 2% of casual blood glucose (level of 126 and 144 mg/dl) had especially marked increases in mortality rates, this increased risk persisted after adjustment for other associated variables (Table 6.13). In conclusion, the IHD, CVD, stroke and all causes mortality risk due to hyperglycaemia is small for the 95% of the population whose casual blood glucose are below the 95 centile. The risk of IHD death more than doubled for the small proportion of the population with blood glucose level above this cut-off point, and study of this group of asymptomatic hyperglycaemic individuals provides clues to the aetiology of atherosclerosis in symptomatic diabetic subjects, and perhaps, in the normoglycaemic population as well.

The detection and adequate treatment of people with the combined risk factors of asymptomatic hyperglycaemia, raised arterial pressure, and also, mass anti-smoking campaigns may prove to be of important in preventive medicine.

CHAPTER 7

GENDER DIFFERENTIAL IN MORTALITY FROM CARDIOVASCULAR DISEASE AND ALL CAUSES IN ASYMPTOMATIC HYPERGLYCAEMICS

SUMMARY: There have been few prospective epidemiological studies of asymptomatic hyperglycaemia as a risk factor for cardiovascular disease mortality in women. Gender-specific mortality rates and relative risks for asymptomatic hyperglycaemics (top 5%) have been compared to normoglycaemics (bottom 95%). Univariate analysis showed that asymptomatic hyperglycaemia was associated with increased risk of all causes, CVD, IHD and stroke mortality in both genders. The degree of this association was greater in women than in men. Using MLR analysis to take account of differences in age, SBP, DBP, serum cholesterol, BMI, and cigarette smoking, high casual blood glucose levels was still a risk factor for cardiovascular disease mortality in both genders. It was also a risk factor for all causes, IHD and stroke mortality in women but not in men. This study shows that to a lesser degree asymptomatic hyperglycaemia shows the same gender differentials in risk of mortality as have been demonstrated amongst known diabetics (162, 164).

CONTENTS

CHAPTER 7

7.1. INTRODUCTION

In industrialized communities, women live longer than men and their age-specific death rates are lower for most causes of death, particularly for IHD (94), a difference which is not completely explained by demographic, psychosocial, behavioural, or biochemical differences between the genders (53, 54, 177). Several studies have shown that clinically manifest diabetes mellitus is connected with an increased risk of premature death, especially from CVD, (141-147, 178) that is not entirely explained by differences in blood pressure or plasma lipid (144). In spite of some controversies in the literature, most studies (162, 164, 179, 180) show that female diabetics have a larger excess of IHD mortality than male diabetics, in comparison with the general population, whereas the excess of cerebrovascular disease mortality of diabetics is equal for both genders. The reason for the greater susceptibility of diabetic women to cardiovascular mortality is not clear (181, 182). However, diabetes appears to reduce the favoured status of women (147, 183). Indeed diabetes (164, 184) and glucose intolerance (36) appear to be weak risk factors for men while for women diabetes is a potent risk factor -even when allowing for other standard cardiovascular risk factors (164, 184). Among asymptomatic hyperglycaemic subjects evidence for gender differences is scant and contradictory. Most of the prospective epidemiological studies concern asymptomatic hyperglycaemia as a probable CVD risk factor only in men, and literature for women is scant. Few prospective

epidemiological studies have addressed themselves to the gender differences in coronary, cardiovascular, stroke or all causes mortality among asymtomatic hyperglycaemic individuals. Because relatively fewer women are studied, any possible difference between the genders may be overlooked. For example, of the 15 studies participating in the International Collaborative Study examining the role of blood glucose as a risk factor for CVD, all of them include only men. The Bedford (178) study showed a higher cardiovascular and overall causes death rate in females than in male "borderline diabetics" and diabetics, particularly in women beyond 45 years of age, the relative excess of IHD mortality associated with impaired glucose tolerance being more marked in men than women. The 10 year follow-up of the Bedford cohort found that borderline post-challenge hyperglycaemia (120-199 mg/dl) carried an excess risk of IHD mortality, but only in women (31). In Tecumseh (185) cross-sectional studies found the relative excess of IHD mortality associated with impaired glucose tolerance to be more marked in men than women. The Chicago Heart Association Detection Project In Industry (186) indicates that symptomless hyperglycaemia was associated with an increased risk of death from IHD. The extent of this association was greater in women than men with regard to relative risk.

The present study examined gender differential in overall, CVD, IHD and stroke mortality among asymptomatic hyperglycaemic subjects compared to normoglycaemic individuals, while simultaneously controlling for several

risk factors analysed in the previous chapter. This study focusses on whether asymptomatic hyperglycaemia displays the gender differences as found in diabetes or the mortality rates found in the general population, independent of established major risk factors.

7.2. ANALYSIS

The gender differential in mortality is assessed by the ratio of male-to-female age-adjusted rates. Two types of statistical analyses are presented in this chapter: relative risks based on age-adjusted mortality rates and independent relative risks determined by a multivariate technique which simultaneously adjusts for other covariables. Significance levels for the former analyses are based on Mantel-Haenszel chi-square statistics (156).

To determine if the increased mortality in women was due to a greater prevalence of risk factors at baseline, the gender specific prevalence and mortality rates for all causes, CVD, IHD and stroke were determined for each category of risk factor, as was the gender ratio of mortality rates. For this analysis, age was included as a continuous variable, while the other risk factors were dichotomized according to frequently used arbitrary cut-points in the following way: Blood glucose (<126 mg/dl, ≥ 126 mg/dl), SBP, (<160 mmHg, ≥ 160 mmHg), DBP, (<95 mmHg, ≥ 95 mmHg), serum cholesterol (<250 mg/dl, ≥ 250 mg/dl), BMI (<27 Kg/m^2, ≥ 27 Kg/m^2), cigarette smoking habit (smoker, non-smoker).

7.3. RESULTS

There were 277 asymptomatic hyperglycaemic and 4,419 normoglycaemic men and 214 asymptomatic hyperglycaemic and

5,500 normoglycaemic women in the study population. Gender specific characteristics of the asymptomatic hyperglycaemic group and normoglycaemic group have already been shown in Table 6.12. Asymtomatic hyperglycaemic women were older (P<0.001) and had a higher SBP (P<0.001) than normoglycaemic women. Asymptomatic hyperglycaemic men were slightly older (P<0.08), had a higher SBP (P<0.001) and also greater BMI (P<0.05) than normoglycaemics. There are no significant differences between asymptomatic hyperglycaemics in men or women for mean DBP, mean serum cholesterol or proportion of cigarette smokers. In both groups men were more likely than women to smoke cigarettes (P<0.01) and to have low cholesterol levels (P<0.01).

As shown in Table 7.1 there were 880 deaths in the male normoglycaemic group of which 454 (51.6%) were attributed to CVD and 329 (37.4%) to IHD and 76 (8.6%) to stroke. Among asymptomatic hyperglycaemic men, 37 of the 63 deaths (58.7) were attributed to CVD and 32 (50.8%) to IHD and 3 (4.8%) to stroke. Among females there were 591 deaths in normoglycaemics of which 244 (41.3%) were attributed to CVD and 162 (27.4%) to IHD and 68 (11.7) to CVA. Among female asymptomatic hyperglycaemics, 28 of the 40 deaths (70%) were attributed to CVD, and 12 (30%) to IHD and 5 (12.5%) to stroke. Both asymptomatic hyperglycaemic men and women had an increased risk of death from overall causes as well as CVD and IHD. Asymptomatic hyperglycaemic men had 1.11 times the age-adjusted overall death rate of normoglycaemic men and 1.25 times the age-adjusted CVD death rate and 1.47 times the

age-adjusted IHD death rate and 0.70 times the age-adjusted stroke death rate. Asymptomatic hyperglycaemic women were generally at greater risk compared to normoglycaemic women, with a risk ratio of 1.55 for all causes, 1.57 for CVD, 1.69 for IHD and 1.58 for stroke.

There was no significant difference in the total mortality rate amongst asymptomatic hyperglycaemic men vs. asymptomatic hyperglycaemic women (1.41 age-adjusted risk ratio), while normoglycaemic men had almost twice the death rate of normoglycaemic women (Mantel-Haenszel X^2 =176, df=1 P<0.0001). However, both asymptomatic hyperglycaemic and normoglycaemic men were at significantly greater risk of death from CVD, IHD, and stroke than women, in accordance with the well established fact that men are much more vulnerable to all causes, CVD, IHD, and stroke than women. The gender differential was somewhat smaller for the asymptomatic hyperglycaemic group. Asymptomatic hyperglycaemic men had almost twice the CVD and 2.5 times the IHD death rate of asymptomatic hyperglycaemic women (13.9/6.9=2.0 CVD age-adjusted risk ratio, 12.1/4.9=2.47 IHD age-adjusted risk ratio), while normoglycaemic men had almost 2.5 times the CVD and 2.8 times the IHD death rate of normoglycaemic women (11.1/4.4=2.52 CVD age-adjusted risk ratio, 8.2/2.9=2.83 IHD age-adjusted risk ratio).

Chi-square statistics reveal the difference in percentages of SBP in male and female hyperglycaemics and male smokers and the obese compared with normoglycaemics as statistically significant as noted in Table 7.2. Table 7.2 also shows that the percentage of smokers and BMI$\geqslant$27

is higher in male hyperglycaemics while the percentage of serum cholesterol and SBP is higher in the high risk category for female hyperglycaemics. In the normoglycaemic group the percentage of DBP, cigarette smokers and BMI in the high risk categories were higher in males than females while the percentage of serum cholesterol and SBP was higher in females than males.

7.3.1.Multiple Logistic Regression Analysis

In the first analysis using MLR, blood glucose was studied as a predictor of mortality without adjustment for other important cardiovascular risk factors but with age-adjustment (Table 7.3). The crude logistic coefficient for blood glucose showed an association with all four categories of death for both genders. There was a stronger association for females judging by the level of significance and the larger logistic coefficients. After age-adjustment the regression coefficients were less in both genders and blood glucose showed an association with IHD and CVD deaths in both males and females, while the association with all causes and stroke mortality in males was not quite statistically significant ($P<0.1$). After age-adjustment females still show stronger associations judging by level of significance and larger logistic coefficients.

Table 7.4 contains the results of MLR analysis when both genders are considered separately with adjustment for other confounding factors. The purpose in adjusting for multiple risk factors was to examine the possible role of these traits in explaining any observed difference in age-

adjusted mortality among both genders. In comparison with the data in Table 7.3 (which does not take into account the effect of associated factors) shown that blood glucose contributes to CVD mortality independent of the other risk factors in both genders. Casual blood glucose contribute to overall causes, IHD and stroke mortality independent of the other risk factors only in women. After adjustment for other cardiovascular risk factors the regression coefficient for blood glucose decreased minimally for males and females. Very little of the effect was lost when other major risk factors were taken into account judging from the modest reduction in the regression coefficient in the multivariate as compared to the univariate analysis. Most of the decreased effect was caused by age-adjustment. After adjustment for age and six other CVD risk factors high blood glucose levels had an excess in CVD mortality when compared to low blood glucose levels and the excess was greater in women (estimated risk ratio=1.17) than in men (estimated risk ratio=1.10). As seen in Table 7.4 casual blood glucose along with age, cigarette smoking and blood pressure was one of five statistically significant independent predictors of CVD mortality in both genders while for all causes IHD and stroke blood sugar was significant only in women. In this model, the contribution of casual blood glucose to CVD mortality was greater in women. Using the same adjustment to assess all causes, IHD and stroke mortality risk in high blood glucose level vs. low blood glucose level results showed once more that the relative risk was greater in women than men (estimated relative risk=1.05, 1.09, 1.13 for men and 1.15, 1.21,

1.20 for women all causes, IHD and stroke mortality respectively).

Blood glucose level was an independent contributor to IHD mortality, along with age, serum cholesterol, SBP and cigarette smoking in women (Table 7.4). In men age, SBP, DBP, serum cholesterol and cigarette smoking were independent contributors to IHD mortality. Blood glucose level was also an independent contributor to stroke mortality, along with age, DBP, cigarette smoking and BMI, while in males only age, SBP, DBP and cigarette smoking contributed to stroke mortality.

However, the risk for high blood glucose was not significantly different after adjustment from that of low blood glucose in men who died from all causes, IHD and stroke. These findings indicate that asymptomatic hyperglycaemia is probably associated with an increased risk of all causes, IHD and stroke death due largely to changes in risk factor status. Results of MLR (Table 7.4) agree with the above finding in that asymptomatic hyperglycaemia was not independently associated with all causes IHD and stroke mortality in men when other risk factors were taken into account. The relative risk of hyperglycaemic women was also reduced with multiple risk factor adjustment, but remained significantly greater than 1.0.

Ratios of risk for gender were determined for asymptomatic hyperglycaemics (upper 5% of casual blood glucose distribution) only, in order to determine the contribution of female gender to mortality in symptomless

hyperglycaemics. As was shown in Table 6.14, gender was a statistically significant risk factor for CVD ($P<0.05$) and IHD ($P<0.05$) mortality with an estimated adjusted ratio of risk for gender of 1.99 for CVD and 2.39 for IHD mortality. However, gender was not a statistically significant predictor of overall causes of death and stroke mortality.

7.4.DISCUSSION

In autopsy studies (181, 182) as well as clinical (104, 187, 188) and epidemiological (31, 141, 179, 180) studies a greater excess of IHD mortality in diabetic women than in diabetic men is shown. However, the extent to which women lose their marked relative protection seems to vary a great deal among studies. In some circumstances the protection was completely removed (189). In others, diabetes exerted a similar impact on men and women (190). Many of the early studies were based on patients identified in hospital, leading to doubts as to the representativeness of the sample. The few population-based prospective studies (164, 165, 186, 191) yielded data indicating that the relative impact of diabetes on IHD mortality is greater for women than men.

Inconsistency was also noted in multivariate analyses in terms of the independent effect of diabetes. While the Framingham study (165) showed an independent effect only for women, the Chicago Heart Association Detection Project in Industry (186) and Rancho-Bernardo Study (191) found that diabetes appeared to be independently associated with IHD mortality in both men and women. In spite of the inconsistencies mentioned, these studies agree that

impaired glucose tolerance is a greater cardiovascular risk factor in females, compared to males.

Most epidemiological studies of symptomless hyperglycaemia and mortality were based on male populations. All of the Collaborative Group studies were based on male populations (36). The only prospective population based study of asymptomatic hyperglycaemia in United Kingdom which include both genders was the Bedford study (178). The Bedford study (178), showed a higher CVD and overall death rate in females than males in "borderline diabetics" and diabetics, particularly in women beyond 45 year of age. In the Busselton Study (167) in Australia the age and gender specific upper 20th percentile levels for the one-hour blood sugar showed a borderline significant risk ratio only for women aged 60-69 (12 years IHD and CVD mortality) and for men of all ages (12 years CVD mortality). Higher risk ratios and significance levels are achieved when the cut-off point chosen approaches the diabetic level (200 mg/dl). It must be stated however, that in the Busselton Study a MLR was not performed and so the independence of blood sugar as a risk factor was not demonstrated, nor was there any evidence that lowering blood sugar levels improved the outlook in relation to mortality or morbidity from CVD.

The role of asymptomatic hyperglycaemia as part of the risk of developing IHD has been extensively studied, with inconsistent results (36, 144, 184). It is not clear whether asymptomatic hyperglycaemia is an independent risk factor for cardiovascular disease. The inconsistencies may

be due in part to the different methods used for characterising an individual's glucose level and to the high degree of misclassification into hyperglycaemic and normoglycaemic groups. It has been demonstrated (192) that one fasting or post load plasma glucose is limited in its ability to validly characterise a person's glycaemic status, because its intra-individual variation is relatively large in comparison to its inter-individual variation. Nevertheless, the univariate and bivariate analyses of the present paper showed in a cohort of middle-aged men and women that asymptomatic hyperglycaemia defined by the upper 5% of single casual blood glucose distribution, is associated with an increased risk of all causes, CVD, IHD and stroke mortality in both genders. The degree of this association was greater in women than in men in regard to relative risk. This finding is confirmed by the Chicago Heart Association Detection Project in Industry (186) for IHD mortality. However, male/female age-adjusted relative mortality risk was of greater magnitude in men than in women except for hyperglycaemic subjects who died from stroke. Of course the number of stroke deaths in hyperglycaemic group was too small and statistical analysis was unstable. In multivariate analysis the risk of CVD mortality for both men and women and overall causes, IHD and stroke mortality only for women with high blood glucose level was significantly greater than that for those with low blood glucose level after taking into account age SBP, DBP, serum cholesterol, BMI, and cigarette smoking: -i.e casual blood glucose was apparently an independent risk factor for CVD mortality in

both genders and for all causes, IHD and stroke mortality in women, although not in men. The independent effect of diabetes was consistently illustrated in women, but not in men. The fact that asymptomatic hyperglycaemia was an independent risk factor for cardiovascular in women, but not in men, underscores the above conclusion. Standardisation for age, SBP, DBP, serum cholesterol level, cigarette smoking and blood glucose level reduced the overall mortality, CVD and IHD gender differential, giving an adjusted relative risk of 1.05 for men and 1.15 for women who died from all causes 1.10 and 1.17 for men and women who died from CVD and 1.09 and 1.21 for males and females who died of IHD and 1.13 and 1.20 for those who died of stroke. However, in a gender specific MLR model, blood glucose was an independent predictor of all causes, IHD and CVA only in women. In CVD mortality it was a predictor of death for both genders. For single casual blood glucose measurement and its association with an increased all causes, IHD and stroke mortality for women -but not for men- the effect was explained by the other risk factors.

The excess mortality in women could not be explained totally by differences in blood pressure or smoking habits at baseline, though it remain possible that other risk indices not measured might have accounted for the observed excess mortality. The reason why asymptomatic hyperglycaemic women show a greater vulnerability to CVD mortality remains unclear. In reviewing all the possible contributing factors, it was not possible to explain the

gender difference. Even accounting for all of the relevant factors together we can not explain entirely why asymptomatic hyperglycaemia in general and women in particular show a greater incidence of IHD, CVD, and overall mortality. Multivariate analysis taking these into account, shows the gender as a predictor of CVD, IHD and all causes mortality. The interaction term for the whole study group showed that there was interaction between gender and blood glucose, but not in the model for asymptomatic hyperglycaemic group.

This study confirms that the gender differential of the upper 5% of casual blood glucose distribution in the less extent follows the pattern of gender differences of diabetics as reported by Framingham (162) and Evan County (164) rather than the general population.

The present report demonstrates in a 10-14 year follow-up an excess risk of CVD mortality amongst the upper 5% of casual blood glucose distribution, and that it is of greater magnitude in women than men.

CHAPTER 8

INTERACTION BETWEEN ASYMPTOMATIC HYPERGLYCAEMIA AND BODY MASS INDEX IN THE PREDICTION OF "ALL CAUSES" AND CARDIOVASCULAR MORTALITY RISK

SUMMARY: The association between blood glucose level and cardiovascular and all causes of death according to BMI has been analysed. Associations between BMI and all causes of death were U-shaped. There was no relationship between BMI and CVD deaths for both normoglycaemics and hyperglycaemics.

An MLR analysis was used to test the interaction of casual blood glucose level and Quetelet Index in the prediction of death, particularly cardiovascular risk. These analyses showed that BMI on initial examination is not a predictor of cardiovascular deaths or IHD deaths 10-14 years later independently of age, gender, serum cholesterol, SBP, DBP, cigarette smoking and blood glucose level. BMI was slightly negatively associated with overall causes of death and CVA deaths. This relationship was dependent on smoking as an interaction term for overall causes and gender and age for cerebrovascular disease deaths. This analysis demonstrates no significant interaction between BMI and casual blood glucose level. This suggests that an increasing trend of relative risk of cardiovascular death with increasing BMI is not further supported by the data when adjustment has been made. Intervention in corpulent subjects to well established risk factors such as cigarette smoking, hypertension, hyperglycaemia and hypercholesterolaemia, appear to be more advisable goals than purely reducing weight, in the primary prevention of cardiovascular death.

CONTENTS

CHAPTER 8

8.1. INTRODUCTION

Many studies have shown that the incidence of certain types of CVD, particularly IHD and stroke is greater in heavier people (112, 193-197). Obesity is associated with elevated blood pressure, blood lipids and blood glucose (198-203), and changes in body weight are coincident with changes in these risk factors for disease (204, 205). Nevertheless, it is the well-known relationship of other cardiovascular risk factors with obesity that makes a positive association of obesity with the risk of IHD biologically plausible.

Obesity has long been implicated in the aetiology of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance (144, 171, 172, 206-208). Thus, the consensus has been that the increased risk among obese people is primarily due to the influence of the associated risk factor profile and not to the degree of obesity per se. As shown by the results of some epidemiological studies, blood glucose level could be a cardiovascular risk factor (36).

On the other hand, in spite of the univariate positive association of BMI with CVD risk, weight is generally not an independent predictor when blood glucose and other risk factors are considered simultaneously. A notable exception is the significant independent association between BMI and CVD mortality reported in the Framingham study after a 26 years follow-up (209). A question which has not yet been fully answered is whether the strength of the relationship between the degree of

asymptomatic hyperglycaemia and CVD is independent of weight.

In this report, this question was considered by analysing cardiovascular mortality in relation to casual blood glucose level and BMI in a representative sample of a middle aged Scottish population in the west of Scotland.

8.2. ANALYSIS

In both genders and in each of the 10 groups defined by the quintile of BMI (males <22.9, -24.8, -26.5, -28.4, ≥28.4 and females <22.0, -24.0, -26.0, -28.7, ≥28.7) and the presence or absence of hyperglycaemia, the death rate is the number of deaths divided by the number of person years of observation in that group. In each quintile of BMI, the relative risk associated with hyperglycaemia is the ratio of death rates in the presence or absence of hyperglycaemia. Mortality ratios for each of the higher quintiles were relative to mortality in the lowest quintile.

8.3. RESULTS

In females, BMI increased slightly with age, from a mean of 25.1±SD 4.0 Kg/m^2 at ages 45-49 up to 26.3±4.7 Kg/m^2 at ages 60-64. In males, the mean BMI did not depend on age, overall mean for males was 25.8±3.4. The mean BMIs were slightly higher in males than females until age 55, after which females had a slightly higher mean BMI.

Table 8.1 shows the number of individuals at base-line, the number of deaths during the period of follow-up, the age-adjusted death rate and rate ratio and the blood glucose characteristics of the subjects in each quintile

of BMI for males and females.

Overall age-adjusted death rates have a U-shaped distribution, being highest in the lowest quintile and lowest in the fourth quintile of BMI for males and the third quintile for females. The patterns at different ages were distinctive, but were however, approximately similar in both genders. As shown in Figure 8.1, in the 45-49 year age group overall mortality decreased from the lowest to the highest quintile of BMI. The U-shaped distribution became apparent after the age of 50. Increasing age was accompanied by an increasing relative risk for the thinnest men and women. Table 8.1 also shows higher mortality in the top and bottom quintiles of BMI for males and females for CVD deaths and IHD deaths but less so for CVA deaths. The mortality ratio of the age adjusted rate for males rose with increasing overweight, IHD mortality in the highest quintile being 45% higher than in the lowest. In females, the IHD mortality in the highest quintile was the same as in the lowest. However as noted in Figure 8.1 the pattern of IHD mortality in different ages was distinctive. In the 45-49 year age group mortality increased from the lowest to highest quintile of BMI in males but not in females, the excess mortality in the heaviest women became apparent after the age of 50. The prevalence of hyperglycaemia also gives a J-shaped distribution being lowest in third quintile in both genders. The mean level of blood glucose is significantly higher in the 5th quintile of BMI. Table 8.2 demonstrates the overall death rates and CVD death rates, IHD death rates and stroke death rates in normoglycaemic and hyper-

glycaemic males and females by quintiles of BMI and the corresponding relative risk in the study. The relative risks for total and CVD and IHD death rates show an inconsistent association with quintile of BMI in both genders. The number of deaths caused by stroke in the hyperglycaemic group is too small to make any statistical inference, but again relative risk was inconsistent with BMI. The differences of the death rates between quintiles of BMI are statistically significant for all causes, CVD and IHD for normoglycaemic subjects. There were no significant differences of death rates between quintiles of BMI for stroke or hyperglycaemics.

BMI is related to blood pressure, cholesterol concentration, cigarette smoking and blood glucose level. Since the relative risks have not been adjusted for these confounding variables, they are considered now.

For this adjustment and also to test the possible interaction between BMI and further confounding variables, MLR analysis was undertaken. This was to ascertain whether the relationship between BMI and mortality would persist after adjustment for the influence of the coexisting levels of the major CVD risk factors. These include age, gender, SBP, DBP, serum cholesterol, cigarette smoking (no, yes) and blood glucose level. Table 6.13 of Chapter 6, gives the result of the MLR analysis for four death categories. According to the model without interaction, BMI is a significant negative predictor for overall causes of death and CVA deaths but not for cardiovascular and IHD deaths. In the model with

an interaction term, there is a significant association between BMI and smoking as a predictor variable for all causes and IHD death. There is also an association between BMI, gender and age for stroke deaths. There is no interaction between BMI and blood glucose level in either analysis and both variables have independent effects. Because of a possible quadratic (U-shaped) association between BMI and all causes, CVD and IHD mortality, the MLR analysis is repeated entering BMI in a quadratic form (BMI*BMI). Again, there was no association between BMI and CVD and IHD mortality, but a slight negative association with overall death persisted.

8.4. DISCUSSION

This chapter has shown that the degree of obesity in the west of Scotland middle-aged men and women was not an important independent risk factor for CVD and IHD deaths in the absence of other risk factors. It was a long term predictor of overall mortality, dependent on smoking, and CVA dependent on age and gender. Some claim that the observed J or U-shaped relationship with BMI is due to the effects of smoking on body weight (210, 211) but others disagree (212, 213). There was no interaction between blood glucose level and BMI, when standardised for other confounding variables. The highest overall mortality in thin subjects shown in this study was also found by the Whitehall study (213) the American Cancer Society Study (212), Framingham Study (214) and others (215, 216). This highest mortality in leanest individuals could be due to cancer or other causes of mortality which were not studied in this chapter. In the Seven Countries Study (217) a

prospective study of 15 cohorts of men aged 40 to 49 years, the 10 year incidence of mortality attributed to IHD or overall mortality was negatively correlated with BMI, relative weight, or skinfold thickness; none of the coefficients was significantly different from zero. A more recent analysis, based on the 15-year follow-up of the cohort in the Seven Countries Study, again failed to show a significant positive relationship of relative weight to IHD in any population. Relative weight was in fact, a significant negative risk factor in Southern Europe (218). Population studies of obesity and heart disease in North American and European men have been variously interpreted. Keys (218) reviewed data from 13 prospective studies and concluded that only 1 showed a definite univariate relationship between overweight and IHD. Larsson et al. (215) reviewed 37 cross-sectional and prospective studies (including most of those reviewed by Keys) and interpreted most as showing an increased risk of IHD in obese persons, although their own prospective study of 50-year-old men in Sweden found no association of obesity with myocardial infarction or death. More recently Hubert (219) reviewed 10 prospective studies and concluded that 6 showed an independent relationship of some measure of obesity in men with subsequent IHD or myocardial infarction. Barrett-Connor (220) reviewed several of the North American studies which also showed an inconsistent relationship of overweight to the risk of manifest IHD. The Pooling Project (14) reviewed data from 12,381 white men aged 40 to 64 years in eight populations in the United States, who

had been followed prospectively from 4.9 to 9.6 years. The pooled data from five cohorts showed a statistically significant linear relationship of relative weight to subsequent IHD, but results for individual cohorts were different. There is little or no association in the Chicago Western Electric Company or the Los Angeles Heart Studies, a shallow U-shaped association in the Chicago Peoples Gas Study, a threshold effect in Albany and possibly the Minnesota Study of American railroad workers, and a stepwise increase in standardised incidence ratio by increasing relative weight was seen only in the Framingham Study. Although there is an excess risk in the heaviest weight group in five cohorts, confidence limits for risk ratios include 1.0 in four of the risk cohorts. Keys et al. (221), studying the relationship of obesity to the incidence of coronary heart disease in three cohorts of men (American railroad workers, North European men and Southern European men) found that those with a BMI of 27 or greater, relative weight of 110% or greater, or sum of skinfolds of 36 mm or greater had no significant excess risk of death from IHD or definite myocardial infarction.

All studies seem to agree on the risks of severe obesity. With regard to CVD and IHD our results initially support those studies which suggest that obesity is a risk factor. However, obesity is related to blood pressure, hyperlipidaemia and diabetes and impaired glucose tolerance (204) and association with IHD is therefore expected. When controlling for these confounding variables together with smoking habits, age and gender, we found that the independent effect of obesity was negligible.

This is in agreement with the Whitehall Study (213) and also with several others (36).

In International Collaborative Group studies (36) blood glucose level showed statistically significant associations with other risk factors, in particular with BMI and blood pressure, and therefore multivariate analyses were carried out to see whether or not the relationship between blood glucose level and prevalence of ECG abnormalities was independent of these other factors. In the majority of the studies, an independent relationship between blood glucose and the prevalence of ECG abnormalities did not persist in multivariate analyses.

In the multivariate analysis, BMI does not appear as a significant independent predictor in either the CVD or IHD categories.

This report shows that the important independent risk factors for all categories of death were as expected. These were smoking habits, age, gender, blood pressure and blood glucose, plus serum cholesterol for CVD and IHD mortality and a negative association of BMI with stroke and overall causes of death.

The lack of association between obesity and cardiovascular death in the MLR model used in this study could be due to an indirect relationship of both obesity and risk of cardiovascular death to other factors. Overeating may be such a factor, because it is known that overeating results not only in obesity, but also in hyperinsulinaemia, hyperlipidaemia, hyperglycaemia and perhaps hypertension. Another alternative explanation, as

mentioned by Bjorntorp (210), is that " only part of the obesity syndrome is associated with risk of CVD. If this is correct, the risk might be so 'diluted' in the total obese population as to be difficult to discover". However, the influence of obesity as a predictor of cardiovascular mortality is less clear. In this study it did not contribute to prediction when casual blood sugar level, age, gender, serum cholesterol and blood pressure were taken into account.

In conclusion, the results presented in this chapter show that in middle aged men and women in Renfrew and Paisley a substantial decrease in the recommended levels of BMI is unwarranted. Although blood glucose and BMI are predictors of overall death, and blood glucose level is also a predictor of CVD, IHD, and stroke mortality, there is no interaction between them.

CHAPTER 9

GENDER DIFFERENTIAL IN MORTALITY FROM CARDIOVASCULAR DISEASE AND ALL CAUSES

SUMMARY: The gender differential in mortality from all causes, CVD, IHD and stroke during the mean follow-up of 11.6 years (range 10-14 years) was examined among 4,696 men and 5,714 women aged 45-64 at entry in West of Scotland.

A MLR model was used to control the influence of gender, along with seven other cardiovascular risk factors simultaneously. The risk factors considered were age, SBP and DBP, serum cholesterol, casual blood glucose, BMI and cigarette smoking. Both the prevalence of risk factors and relative mortality risk associated with them differ by gender.

Adjustment slightly reduced the gender differential in overall mortality from 2 to 1.9 and from 1.5 to 1.4 for stroke deaths. Multivariate adjustment increased minimally the gender differential for mortality from 2.4 to 2.8 for CVD and from 2.8 to 3.4 for IHD, suggesting that these cardiovascular risk factors do not account for the overall gender difference in mortality rates.

Assessment of other environmental and behavioural risk factors, gender-linked inheritance and differences in hormonal balance and other biological variables and their interaction with each other may more fully explain the gender differential in mortality.

CONTENTS

CHAPTER 9

9.1. INTRODUCTION

In Scotland, as in other industrialized communities, women live longer than men. Their age-specific death rates are lower for most causes of death, particularly IHD. Several explanations have been proposed to account for this gender differential in mortality. The higher death rate for men may be due to biological variation (72, 222), gender linked-inheritance, psychosocial factors or to differences in hormonal balance, environment, or habits (55-57, 223, 224). Women are considered to be biologically "more fit" than men (72, 222) and second, men behave in ways more damaging to health (55, 223). However, some risk factors may be of different importance in men and women. It may be questioned whether this difference between the genders can be explained by differences in known cardiovascular risk factors.

The present study examines the gender differential in mortality from all causes, CVD, IHD and CVA while simultaneously controlling for several cardiovascular risk factors.

9.2. ANALYSIS

The analytical procedure performed in this chapter is the same as in chapter 7.

9.3. RESULTS

After ten to fourteen years follow-up from the initial examination 945 men had died, equivalent to 19.4/1,000 person years of observation. 492 deaths (52%) were attributed to CVD, 362 (38%) to IHD, and 79 (8.3%) to

stroke. Among women 631 (40%) deaths, or 10.8/1000 person year of observation, occurred during the same period, 272 (43.1%) of which were attributed to CVD and 174 (27.6%) to IHD and 73 (11.6%) to stroke.

Age, gender-specific, overall age mortality rates and gender differential for all causes, CVD, IHD and stroke mortality for men and women aged 45-64 years at entry are presented in Table 9.1. As expected, men have higher mortality rates than women and mortality rates increase sharply with age. One measure of the gender differential in mortality is the age-adjusted ratio of male to female death rates. In this study population, the age adjusted relative risk of mortality for men compared to women are 2.0 for all causes, 2.4 for CVD, 2.8 for IHD and 1.5 for stroke deaths. Men have approximately twice the overall death rate and three times higher IHD death rates than women over the 10-14 years follow-up.

To be a confounding variable, a risk factor must be distributed differently among men and women. Differences in distribution of several risk factors among men and women are shown in Table 9.2. A significantly higher proportion of men had smoked cigarettes and had higher than cut-off levels of DBP and of casual blood glucose; while a higher percentage of women had higher SBP and had higher levels of serum cholesterol. There were no gender differences in obesity and the ages of the two gender groups were similar.

The age-adjusted gender differential in mortality for each category of risk factor is presented in Table 9.3. For deaths due to all causes, CVD, IHD or stroke, the

relative mortality risks in both high and low categories of risk factors for men compared to women were greater except in the high category of casual blood glucose which showed a lower stroke mortality rate in men. The number of deaths in this category is too small to make a valid statistical inference.

All causes. Men and women in the high-risk categories of SBP and DBP and cigarette smokers had a greater overall risk of dying from all causes while women, but not men, in the high risk category of casual blood glucose were at greater risk of death.

All cardiovascular disease. Mortality rates for all CVD were significantly greater for smokers compared to non-smokers, for those with higher SBP and DBP, and for men with higher casual blood glucose.

Ischaemic heart disease. Men and women in the high risk categories of SBP and DBP were at greater risk of dying from IHD, while men, but not women, in the high risk category of casual blood glucose, and women who smoked cigarettes or obese, were at greater risk of IHD death.

Stroke. Mortality rates for stroke were significantly higher for men and women who were in the high risk category for DBP and who smoked cigarettes, and for men who were in the high category of SBP. Only one factor, casual blood glucose, showed a lower mortality rate in men than women (relative risk=0.7).

9.3.1.Multiple logistic regression analysis

To determine if the gender differential in mortality is merely a product of difference in the distribution of

risk factors, all eight variables were controlled simultaneously by means of a MLR analysis. The MLR coefficient and approximate relative mortality risks (odds ratio) of each risk factors including gender are presented in Table 6.13 of Chapter 6.

All Causes Mortality: Controlling for age and six other cardiovascular risk factors slightly reduced the gender differential in overall mortality from 2 to 1.9 ($P<0.001$).

CVD and IHD Mortality: Controlling for age and other confounding variables increased the gender differential in CVD and IHD from 2.4 and 2.8 to 2.8 and 3.4 respectively.

Stroke Mortality. After adjustment for age and other confounding variables slightly reduced the gender differential in stroke mortality from 1.5 to 1.4.

Each of the seven variables associated with mortality risk and distributed differently among men and women are potentially confounding variables in the analysis of the gender differential in mortality. However, for each subcategories of these variables, women have lower age-adjusted death rates than men. To remove the possible effect of clustering of these seven cardiovascular risk factors, a MLR analysis was performed for all seven variables for each gender. Through this analysis, the association of each variable with mortality can be determined, independent of the distribution of the other variables.

All Causes: Gender specific MLR analyses of all causes, CVD, IHD, and stroke mortality showed (Table 7.4 of Chapter 7) age, cigarette smoking and SBP to be significant predictors of all causes mortality for both men and

women. Of the factors which demonstrate a statistically significant influence on mortality in both genders, women have higher relative risks except cigarette smoking and age, for overall causes mortality. DBP was a statistically significant predictor only for men while BMI was negatively, and casual blood glucose positively, predictive of overall mortality only in women.

Cardiovascular Disease:. For CVD, analyses demonstrated age, SBP, DBP, blood glucose and cigarette smoking to be significant predictors of mortality for both genders. Serum cholesterol were statistically significant predictors of CVD death only for men.

Ischaemic heart disease. Gender specific MLR analyses of IHD mortality showed age, SBP, serum cholesterol and cigarette smoking to be significant predictors of IHD mortality for both males and females. DBP was statistically significant only for males and blood glucose only for females.

Stroke: The gender specific MLR analyses for stroke mortality showed age, DBP and cigarette smoking to be significant predictors of stroke mortality for both genders; SBP, only for males; and blood sugar and BMI (negatively) only for females.

9.4.DISCUSSION

In this analysis of the middle aged population drawn from Renfrew and Paisley, the cardiovascular risk factors considered do not account for the gender differential in mortality risk over a 10-14 years follow-up period. However it does confirm the findings of others who have

shown the predictive value of the measure of risk factors, age, gender, blood pressure, serum cholesterol, and cigarette smoking.

To understand how the net influence of CVD risk factors can actually increase the mortality risk of males to females, it is necessary to understand how each variable individually affects the gender differential. To be a confounding variable, the CVD risk factors must both be associated with mortality and distributed differently among men and women. All of the seven variables tested are independently associated with mortality except serum cholesterol for stroke death, BMI for CVD and IHD, and SBP for stroke. Among these seven variables, three high risk characteristics are more common in men (smoking, raised DBP and blood glucose levels), while two are more common among women (raised SBP and serum cholesterol). These results reflect those in the Framingham population (224) in which cholesterol level and SBP were higher in women and glucose intolerance was higher in men. In the Rancho Bernardo study (54) cholesterol levels were higher in women and SBP and fasting plasma glucose higher in men. Obesity was not significantly different between the two genders and the ages of the two gender groups in this study were similar. It has also been suggested that high serum cholesterol may be as strong a risk factor in women as in men. The higher relative risk for smoking among men than women in the west of Scotland has been reported in other studies (53-56, 60, 111, 224, 225).

Because of established gender differences in mortality in diabetes and higher prevalence of cardiovascular risk

factors (144), these men and women were not included in this analysis.

In the present study, the gender differential in age-adjusted mortality from all causes is slightly reduced from 2.0 to 1.9 by multivariate adjustment for cardiovascular risk factors. Among variables, the estimated relative risks for all causes mortality for male smokers is considerably higher than female. These differences may reflect higher lung cancer mortality in male smokers. Hammand (60) has examined the gender differences in relation to smoking behaviour utilizing data from the American Cancer Society. He adjusted only for age, concluding that smoking is a risk factor for both genders, but more so for men.

The present study reported a greater than twofold gender difference in CVD and a threefold difference in IHD mortality after multivariate adjustment.

The gender differential in CVD and IHD mortality increased from 2.4 and 2.8 to 2.8 and 3.4 respectively. This does not mean that cardiovascular risks do not influence the gender differential. On the other hand, many of the variables have a marked effect on gender differential. Some increase, while others decrease, the gender differential. However, none of the variables entirely account for the gender differences in mortality. Adjustment for risk factors that are more common among men decreases the gender differential, while adjustment for those that are more common among women increases the difference. If the gender differential in mortality is

merely a product of variations in risk factors, the introduction of all appropriate adjustments should result in a male to female mortality ratio that approaches unity. However simultaneous adjustment for seven cardiovascular risk factors slightly decreases the gender differences in estimated overall mortality and stroke mortality risk, while increasing the estimates for CVD and IHD relative risk. Using Framingham data, Johnson (61) adjusted for age and several biological measurements (e.g., blood pressure and cholesterol), and similarly concluded that IHD mortality for male smokers is considerably higher than for female smokers. Also Waldron (55) suggested that men have higher death rates for arteriosclerotic heart disease in large part because they smoked cigarettes more and because they more often develop aggressive, competitive, coronary-prone behaviour patterns. This finding is not supported in this study. Cigarette smoking is a risk factor for both males and females, but gender differentials of age-adjusted relative risk for all causes, CVD, IHD, and stroke mortality risks for smokers and non-smokers were not different. Smoking may be more severe for men because men who smoke are more likely to drink alcohol while women do either one or the other. After multivariate adjustment the estimated relative risks of CVD, IHD and stroke mortality for female smokers are higher.

Gender differentials in mortality will remain after adjustment for cardiovascular risk factors if women have lower death rates than men for subcategories of the risk factors (this is true for all seven variables), or if the

relative risk associated with the variable is higher for men. The gender differential that remains may reflect either an inherent biological difference between the genders, a difference in behavioural factors or differences in hormonal status or environment, or an interaction of these factors.

Waldron (55) reported that the largest differences between male and female death rates occur for IHD, accidents, suicide, lung cancer and cirrhosis of the liver. She suggested that these causes of death are linked to behaviours which are encouraged or more accepted in males (e.g., smoking, drinking alcohol and work at hazardous job). Bengtsson et al. (104) also reported similar results in their study of gender differential in IHD in 50-54 year old Swedish men and women. They conclude that men's higher rate of IHD are related to their higher rates of smoking and drinking alcohol, higher aggression and achievement scores and greater self reported stress. These authors believe that additional factors also contribute to the observed gender differential in IHD. Wingard et al. (53, 54) also analysed several demographic, behavioural and biological factors and found these factors do not account for the overall gender difference in mortality rates.

A few studies have observed that the male death rate is higher even in prenatal life and infancy (62-64). Since behavioural factors that increase mortality risk do not vary by gender of the foetus, gender differences in rates of miscarriage, stillbirth and early infant death are

presumably due to unspecified biological factors. However, foetal mortality is as high for females as for males in a few geographical areas, for example, Scotland (63). Among adults, a possible biological basis for gender differentials in mortality has been examined through the relationship of hormonal status and IHD. These studies (90, 92) reported that IHD mortality increases among women around the age of menopause and varies by pregnancy history, suggesting that changes in oestrogen or prolactin levels may be the cause. However, increased morbidity and mortality among those receiving oestrogen supplements does not support this hypothesis (93, 94).

The present investigation demonstrates, in a west of Scotland population, a two to three times higher relative risk for men than for women, for both CVD and IHD. This was associated with all the seven cardiovascular risk factors considered, either in high or low categories. This finding is similar to that of the San Fracisco-Oakland study (111).

Several studies (55, 72, 222, 223) have suggested that biological and behavioural risk factors influence mortality risk and the gender differential in mortality. In this study, although gender differences in the prevalence of cardiovascular risk factors and relative mortality risk for each variable are demonstrable, they did not explain the gender differential in mortality from all causes, CVD, IHD and stroke.

Finally, this study confirmed that CVD risk factors are better predictors of CVD in women, than in men, as suggested by the Framingham Study (183).

CHAPTER 10

SYSTOLIC AND DIASTOLIC COMPONENTS OF BLOOD PRESSURE AS PREDICTORS OF ISCHAEMIC HEART DISEASE MORTALITY

SUMMARY: The relative importance of SBP versus DBP in predicting risk of IHD mortality is controversial. The relative importance of SBP compared to DBP and other combinations of SBP and DBP in predicting the risk of IHD mortality have been re-examined. In the 10-14 years follow-up period there were 553 (372 male and 181 female) deaths due to IHD. In a MLR model the predictive value of SBP, DBP, MAP, MAI and PP was examined in relation to IHD mortality after adjustment for age, BMI, casual blood glucose, serum cholesterol and cigarette smoking. While all measures were associated with IHD mortality the risk of IHD deaths was more strongly associated with MAI and SBP alone in both males and females. SBP and DBP together, MAP and PP discriminated future IHD mortality not better than SBP alone or MAI.

CONTENTS

CHAPTER 10

10.1. INTRODUCTION

Blood pressure has been identified as perhaps the most universal contributor to all forms of CVD and one of the strongest predictors for the occurrence of IHD (108, 112-118, 123, 227-228). Although both SBP and DBP are recognized predictors of IHD risk (229, 230) whether SBP or DBP is more important as a risk factor for this disease still remains controversial. Textbooks of clinical medicine (231, 232) and others (233) suggest that DBP is more important.

The assumption that DBP is the chief determinant of cardiovascular morbidity from hypertension is not illogical. The haemodynamic hallmark of essential hypertension is an increase in peripheral resistance that is manifested chiefly by a rise in DBP (124, 234, 235). This viewpoint however, has been questioned and for IHD many epidemiological studies (108, 112, 113-119) favour SBP, although this is not a universal finding (121, 122, 123).

It is possible that both components of the blood pressure contribute to the risk of IHD mortality. Consequently, the ability of other combinations of SBP and DBP to discriminate potential IHD mortality was compared with that of each component of the blood pressure. The parameters of blood pressure examined in relation to IHD mortality in this study included: SBP, DBP, PP (SBP - DBP) MAP (DBP + one-third the PP) and MAI (one-third DBP + two-third SBP). The objective was to compare each of these

components of blood pressure as predictors of IHD mortality.

This study also examines the possible interaction of cardiovascular risk factors with the relative strength of SBP, DBP, and various combinations of SBP and DBP as predictors of death from IHD in males and females separately, in a middle-aged cohort from Renfrew and Paisley in the west of Scotland.

10.2.RESULTS

During follow-up after the initial examination 372 men and 181 women had died from IHD. As expected, the IHD mortality rate increased with age in each gender and men had a higher mortality rate than women (Figure 10.1). Age-adjusted IHD mortality rate in men is about 4 times (8.4/2=4.2) higher than females.

10.2.1.Prediction of IHD Mortality Using Blood Pressure Quintiles

An examination of the gradients of risk of IHD in persons classified according to quintiles of their SBP and DBP, MAP, MAI and PP respectively revealed rather similar gradients of risk as noted in Figure 10.2. When this was adjusted for differences in the age composition and gender of each quintile of the distribution of each blood pressure component, three facts became apparent:

1) Men have higher mortality rates in each quintile than women and the relative risk comparing those in low versus high quintile within each gender was as great in women as in men. There was an increase of about 3 times in age-gender adjusted mortality from the bottom quintile compared to top quintile of blood pressure.

2) There is no critical level of blood pressure evident, the risk being simply proportional to the level from the lowest to the highest recorded, in either gender.

3) Gradient for SBP and DBP, MAP and MAI are quite similar with nothing to suggest a closer relationship to DBP.

10.2.2.Age and Blood Pressure

Tables 10.1 and 10.2 and Figure 10.3 present the effects of age on blood pressure measurements. The expected gradient of increasing level of SBP, MAI, MAP and PP with advancing age was seen in each category for males and females except for the 60-64 year age group in females who died from IHD. In people alive after 10-14 years and who died from IHD, it rises more steeply in women. Females exhibit a lower average SBP, MAI and MAP below age 50-54, after which they overtake and exceed the pressure in males except for PP of survivors which was higher than males in all age groups. The smaller rise was also seen in females' DBP level and there was no rise with advancing age in men who were still alive. The mean DBP rises more steeply in women who have a higher mean DBP after age 60 years before which men have higher DBP. In males who died from IHD there was no relationship between the diastolic level and age. The mean values for SBP and DBP, MAP and MAI were significantly greater for those dying of IHD than for those alive after 10-14 years for all age groups in men and most age groups in women (Table 10.2). The mean standard normal deviate values showed a similar pattern but they showed no general increase with advancing age.

In persons dying of IHD the age-adjusted standard normal deviate for SBP, MAP and MAI was slightly but significantly greater than that for DBP especially in females. Table 10.3 also shows that the mean standard normal deviates for SBP, DBP, MAP and MAI were all significantly greater for those dying of IHD than for those still living. For men and women dying of IHD the mean difference between the standard normal deviates for SBP and DBP was 0.09 ($P<0.06$) for males and 0.15 ($P<0.05$) for females and the mean difference between the standard normal deviates for MAP and DBP was 0.08 ($P<0.05$) for males and 0.11 ($P<0.001$) for females; for MAI and DBP it was 0.09 ($P<0.05$) for males and 0.15 ($P<0.01$) for females respectively. Men and women dying of IHD therefore have a SBP, MAP and MAI that deviates from the mean for their age specific group to a small but significantly greater extent than does their DBP. The PP deviate from the mean for their age-specific group is not significantly different from their DBP. Table 10.4 shows the mortality from IHD in the age-specific and age-adjusted upper quintiles of SBP ($\geq$167), DBP ($\geq$95), MAP ($\geq$118), MAI ($\geq$142) and PP ($\geq$77) and the ratio of these death rates compared with DBP. In males and females at all ages the rate was in favour of MAI, and except for males 45-49, also in favour of MAP. In males at all ages except 50-54 years the rate was in favour of SBP and in females in age group 50-54 and 60-64 was in favour of DBP; in the age group 55-59 the rate was in favour of SBP. In males 45-49 and 60-64 the rate was in favour of PP and in age 50-59 in favour of DBP; in females in all age groups it was in favour of DBP. After

adjustment for age the mortality rates in the upper quintile of SBP and DBP were 13.7 for males and 4.8 for females and 12.8 for males and 4.7 for females death/1,000/person-year respectively. The Age-adjusted rate ratio of 1.07 for male and 1.01 for females suggests that only 7% and 1% more men and women could have been identified as being at higher risk of dying from IHD if SBP rather than DBP had been measured. The age-adjusted rate ratio for male MAP and MAI was 1.08 and 1.07 and for female was 1.03 and 1.11 respectively.

10.2.3.Multiple Logistic Regression Analysis

Age, BMI, cigarette smoking habit, serum cholesterol and blood glucose level may all have been associated with the level of blood pressure at the time of screening in those subjects who eventually died of IHD. On the other hand, the absence of a demonstrable safe or critical level of blood pressure as regards risk of IHD mortality suggests that it is more logical to examine the relative contribution of each blood pressure component through the range of blood pressure rather than in a discrete clinical blood pressure category (e.g."normotensive" vs "hypertensive"). Also SBP and DBP are highly correlated (r=0.66) (Table 10.5), making an assessment of the net effect of each difficult, if not impossible, employing simple categorical cross classification. Consequently, MLR analysis was undertaken to assess the relative contribution of each component of the blood pressure to IHD throughout the range of pressure recorded in the population sample. In the first analysis using the MLR, the SBP,

DBP, MAP, MAI and PP were studied separately as predictors of IHD mortality, without adjustment for other important cardiovascular risk factors (Table 10.6). The logistic coefficients for SBP, DBP, MAP, MAI and PP each showed a strong relationship with IHD mortality in both genders. SBP and MAI show a higher odds ratio than DBP and PP in both genders. Table 10.7 contains the result of MLR analyses when both SBP and DBP are considered simultaneously and each of five blood pressure components separately with adjustment for other confounding factors. In the first analysis using the MLR risk model, SBP and DBP, the PP, the MAP and the MAI were studied separately as predictors of IHD deaths for each gender. The logistic coefficients for the blood pressure measures were determined after adjustment for the effect of age, serum cholesterol, blood glucose, cigarette smoking and BMI on the IHD mortality. In comparison with the data in Table 10.6 (which do not take into account the effect of associated factors) the SBP, DBP, MAP, MAI and PP contribute to IHD mortality risk independent of the other risk factors. Except for male DBP, the SOR for SBP and DBP, PP, MAP and MAI decreased minimally after adjustment for other cardiovascular risk factors. Very little of the effect is lost when other major risk factors are taken into account judging from the modest reduction in the regression coefficient in the multivariate as compared to the univariate analysis. This reduction was higher in females than males. The logistic coefficients for SBP and DBP, the PP, the MAP and the MAI as well as age, cigarette smoking habits and serum cholesterol levels each show a strong

relationship with the IHD death in both genders. Blood glucose illustrated an association with the IHD mortality only in females. BMI was not found to be a significant predictor of the IHD risk in multivariate analysis of either this study or that of Framingham (28) or the Western Collaborative Group Study (119, 236). The fact that all components of pressure contribute to the risk of IHD is very likely attributable to their high correlation of SBP and DBP. The magnitude of the SORs can give an indication of the relative contribution of each component. Table 10.8 summarized Table 10.7 from the view point of ease of comparison and interpretation of the odds ratio of each component of blood pressure. There was interaction between DBP and serum cholesterol and MAP and serum cholesterol in males and PP and smoking in females. Table 10.5 shows the coefficients of correlation observed between the different blood pressure measures and indicates expected close interrelationship. Thus, although each of the five blood pressure measures was found to show a strong relationship to the risk of IHD after adjustment for other risk factors, further joint analysis of the SBP and DBP measures is required to determine which measures have direct strength. The bottom of Tables 10.7 and 10.8 also display the results of multivariate analysis using the multiple risk model, in which SBP and DBP are considered together to determine their standardised predictive strength for the risk of IHD death in males and females. Only minor changes were noted in the predictive strength of these adjusted factors compared to the results

shown for only SBP or DBP analysis. In females, the DBP was found to be not significantly associated with IHD death. In males there is statistically significant interaction between SBP and DBP. In both males and females respectively SBP with odds ratios of 1.27 and 1.22 ($P<0.001$) is a slightly better predictor of IHD death than is the DBP with standard odds ratios of 1.24 ($P<0.01$) and 1.11 ($P=0.2982$).

10.3. DISCUSSION

Although both SBP and DBP are recognized predictors of IHD risk (230, 231), the primary purpose of the present analysis was to examine the comparative predictive strength of each component of blood pressure in males and females separately. However, this study as well as most other studies (108, 112-119, 123, 227-228, 230, 236) suggest that the IHD mortality risk is significantly and independently related to the antecedent blood pressure measurements and that this risk is proportional to the blood pressure level. The risk of increased IHD mortality appeared to be related even to a single blood pressure determination, despite the effects of lability, diurnal variation, artifacts of measurements (fat-arm artifacts, technical errors in measurement, unconscious digital selection (237)) and the response to therapy (108, 238).

At any age and at any blood pressure, IHD mortality in men exceeds that in women but this does not mean that women tolerate hypertension better than men. This is revealed best by an examination of the coefficients for the regression of IHD mortality on blood pressure, which indicate values almost as large for women as men in both

univariate and multivariate analysis (Tables 10.6, 10.8). The reasons for the lower IHD mortality in women are not clear.

The standard normal deviates were calculated according to the Whitehall Criteria (120), to provide an estimate of the capacity of each component of the blood pressure in order to discriminate those who died of IHD from the total population under study. Table 10.9 summarises the standard normal deviate separating survivors from men who died of IHD and standardised odds ratio and mortality in the upper quintile of SBP and DBP in this study and the Whitehall study. On the whole, both studies agree that SBP appeared to be the better predictor than DBP at all ages except age 40-44 in the Whitehall Study and age 50-54 in this study. This was supported by MLR analysis and the comparison of mortality from IHD in the upper quintile of blood pressure in both studies. Whereas the Framingham Study (115) compared levels of age specific mean blood pressure between groups dying of heart disease and those still living. Neverthless their finding for SBP, DBP, MAP and PP for males and females are similar to our findings. However, in this study the differences between SBP and DBP for males is small (0.09) but is neverthless the same as the Whitehall male study (0.07). On the whole, SBP appeared to be the better predictor of IHD in both genders. This was supported by MLR analysis and the comparison of mortality for IHD in the upper quintile of blood pressure as well as the Whitehall Study (120), the Western collaborative Group Study (119), the

Framingham Study (108) and others (112-118). Univariate analysis of mortality from IHD in the upper quintile of SBP and DBP were also shown in the IHD, in favour of SBP in both genders. In males, when analysed separately, the SBP, DBP, MAI and MAP showed essentially the same predictive strength, while the PP showed somewhat less relationship to IHD mortality. In females, when analysed separately, SBP, MAI and MAP were found to be stronger predictors of the IHD mortality than the DBP or PP. However when each is considered alone, MAP and MAI as a measure of blood pressure is a slightly better indicator of risk than SBP, but all SBP and MAI and MAP were better predictors of risk than DBP alone. When either SBP or DBP is adjusted for the others, the standardised odds ratio becomes 1.27 and 1.22 for males and females' SBP and 1.24 and 1.11 (not significant) for males and females' DBP with interaction between SBP and DBP in males. In both males and females, when analysed separately and both together, SBP was found to be a slightly stronger predictor of the IHD death than the DBP, although the differences in predictive strengths were not large. There are some factors which may contribute to the observation that SBP is slightly superior to DBP as a predictor of death from IHD as stated by the most of the same studies. One explanation is that the greater variability of SBP, causing a larger standard error of its measurement, does not allow the statistical separation of the IHD and non-IHD group. With ageing a proportionally greater increase in SBP than DBP occurs. The greater difference in mean SBP between the groups compensates for the larger variance in

the measurement of SBP. As systolic level depend partly on arterial compliance (239) they may provide a better reflection of the degree of underlying arterial disease. The failure of DBP to excell in predicting IHD may in part be due to the greater inaccuracy in measuring DBP and to the narrower range of values available compared to SBP.

An interaction term was introduced between each component of blood pressure and BMI in addition to age, serum cholesterol concentration, blood glucose level, cigarette smoking habits in MLR model; under this circumstances and running the analysis separately for men and women the interaction term between BMI and the blood pressure component was non-significant in both males and females. Hence, this study does not support findings of those (122, 240) that claimed an interaction between blood pressure and BMI.

This results supported findings of other workers (108, 112-119) who have suggested that SBP may be a better predictor of IHD mortality.

The present data do not suggest a declining importance of DBP, but suggest an increase in importance of SBP and MAI in both males and females for IHD.

CHAPTER 11

SYSTOLIC AND DIASTOLIC COMPONENTS OF BLOOD PRESSURE AS PREDICTORS OF STROKE MORTALITY

SUMMARY: The relative importance of SBP versus DBP in the prediction of stroke have been re-examined.

In the follow-up period 10-14 years; (mean 11.6) there were 160 deaths (80 male; 80 female) from stroke. SBP and DBP are strongly correlated in both genders ($r=0.66$, $P<0.001$) but in the relationship with stroke mortality there was difference in males and females.

In a MLR model the predictive value of SBP, DBP, MAP, MAI and PP was examined in relation to cerebrovascular disease mortality, after adjustment for age, gender, BMI, casual blood glucose, serum cholesterol and cigarette smoking. All blood pressure measures were associated with stroke mortality; in females the risk of stroke mortality was more strongly associated with DBP; in males SBP and DBP have the same predictive strength for stroke death and MAP and MAI have stronger association than either SBP and DBP.

These findings suggest that the predictive strength of SBP and DBP for stroke mortality may depend on age and gender. In middle-aged men and women in Renfrew and Paisley, Scotland, the general concept that DBP is more important than SBP is supported by data on stroke death in women, while in men the DBP was as good a predictor of stroke mortality as SBP.

CONTENTS

11.1. INTRODUCTION

Blood pressure is the most potent risk factor for the development of stroke (108, 125, 197, 229, 241-243). Although both the systolic and diastolic components of blood pressure are recognized predictors of stroke risk (125, 229, 230), whether SBP or DBP is more important as a risk indicator still remains controversial.

The assumption that DBP is the most important predictor of cardiovascular morbidity from hypertension is supported by the fact that essential hypertension is associated with an increase in peripheral resistance which is manifested chiefly by a rise in DBP (234, 235). This viewpoint however, has been questioned (125, 126, 244-249) and for cerebrovascular disease two epidemiological investigations (124, 126) have favoured SBP as the strongest predictor.

In a longitudinal study of a well-population of 10,541 men and women in middle life we have re-examined the predictive value of several combinations of SBP and DBP measurements, made at entry to the study, for stroke mortality.

11.2. RESULTS

11.2.1. Blood Pressure and Stroke Death

Age and Blood Pressure: Tables 11.1 and 11.2 and Figure 11.1 indicate the relationship of age to blood pressure measurements. In survivors at follow-up the expected age-related gradients of SBP, MAP, MAI and PP, at entry, was seen in each category for both males and females. This relationship is stronger for females than

females. This relationship is stronger for females than males. In persons who died from stroke the mean SBP, MAP and MAI levels, at entry, were widely separated and approximately parallel in males and females in the younger age groups and closer, or crossover with lower levels, in older males. In those who were dead at follow-up males showed higher pressure levels at entry, except for PP which was higher in females in all age groups apart from the extreme ages. In survivors, entry DBP was lower in females than males up to the 55-59 age-group. In males who died from stroke, there was no consistent relationship between the DBP level and age, while in females higher levels were associated with advancing age. Overall the mean values for SBP, DBP, MAP, MAI and PP at entry, were significantly greater for those dying of stroke than for survivors after 10-14 years. The most marked age-specific differences were for males aged 55-59 and 60-64. But for MAP and DBP the mean values were very high for younger ages too.

The mean SND values showed a similar pattern to the blood pressure component but no consistent increase with increasing age. In both men and women who died from stroke the overall age-standardized normal deviates for DBP were slightly greater than SBP, MAI and PP, but there is nothing to suggest that DBP was a better predictor of stroke death than MAP (Table 11.3). The mean SND for SBP, DBP, MAP and MAI were all significantly greater for those dying of stroke than for those still living at the time of follow-up. Both men and women dying of stroke have a DBP that deviates from the mean for their age-adjusted group

to a small and not significantly greater extent than does their SBP, MAP, and MAI, except PP in men.

Prediction of Stroke Mortality Using Blood Pressure Quintiles: Table 11.4 shows the mortality from cerebrovascular disease in the age specific and age-adjusted upper quintiles of SBP (≥167), DBP (≥95), MAP (≥118), MAI (≥142) and PP (≥77), and the ratio of these death rates to those associated with DBP. In males, at all ages except 55-59, the death rate was most closely related to MAP. Similarly, except for the 45-49 age-group, the death rates were more closely related to MAI and SBP than to DBP. In females at all ages, except 55-59 years, the death rates were most closely related to DBP compared to SBP or MAI. The age-adjusted rate ratio of using SBP, MAP and MAI to predict death rates suggests that 26%, 10% and 18% more men respectively could have been identified as being at higher risk of dying from stroke than if DBP had been used alone. For females, using DBP alone suggests that respectively 34%, 5%, 22% and 31% more women could have been identified as being at higher risk of dying from stroke than if SBP, MAP, MAI, or PP had been used.

1.2.2.Multiple Logistic Regression Analysis

Age, BMI, cigarette smoking, serum cholesterol and blood glucose level may all have been associated with the level of blood pressure at the time of screening in those subjects who eventually died of stroke. On the other hand, the high correlation between SBP and DBP estimates (r=0.66) (Table 10.5), makes an assessment of the net effect of each difficult, if not impossible, by employing

simple categorical cross tabulation.

MLR analysis was undertaken to assess the relative contribution of each blood pressure variable to stroke mortality throughout the range of pressure recorded in the population sample. First the SBP, DBP, MAP, MAI and PP were studied separately as predictors of stroke mortality, without adjustment for other main cardiovascular risk factors (Table 11.5). The logistic coefficients for SBP, DBP, MAP, MAI and PP each showed a strong relationship with stroke in both genders. The SOR are largest for SBP and MAI in men followed by MAP and DBP. In women the SOR is highest for MAP followed by DBP, MAI and SBP, whereas PP is associated with the least excess risk in both genders.

It is conceivable, although unlikely because of the strength of the relationship, that the association of elevated blood pressure with increase risk of stroke mortality derives at least in part from factors related both to blood pressure and to the risk of stroke mortality. This was assessed by including age, serum cholesterol, blood glucose, BMI and cigarette smoking habit in the MLR. The results (Table 11.6) indicate that except PP in females, all components of blood pressure are potent independent predictors of stroke mortality, after allowing for the effects of other risk factors.

The SORs provide an indication of the relative contribution of each component.

When both SBP and DBP considered simultaneously, there was interaction between DBP and age and SBP and cigarette smoking in females. The fact that all components

of pressure contribute to risk of stroke mortality is very likely due to the high correlation between SBP and DBP. Table 10.6 shows the coefficients of correlation observed between the different blood pressure measures and illustrates the expected close interrelationship. Thus, although each of the five blood pressure measures was found to show a strong relationship to the risk of stroke after adjustment for other risk factors, further joint analysis of the SBP and DBP measures is required to determine which measure has the most power. Interpretation of the results at the foot of Table 11.6 is focussed on the analysis which include both SBP and DBP. Although major changes were noted in the predictive strength of these adjusted factors compared to the results shown for only systolic and diastolic analysis, the overall results are the same. In females SBP was not a statistically significant predictor of stroke death and there was an interaction between DBP and age. However, in males DBP, with a SOR of 1.41 ($P<0.05$), shows the same predictive strength for stroke death as SBP, with a standard relative risk of 1.39 ($P<0.05$). For females, DBP with SOR of 1.78 ($P<0.001$) is a better predictor of stroke deaths than SBP with a SOR of 1.02 ($P=0.78$).

11.3. DISCUSSION

Both SBP and DBP are recognized predictors of stroke risk (229, 230) but many authors have considered the diastolic component to be the most important. Recently this view has been questioned. The purpose of the present analysis was to examine the comparative predictive

strength of each component of blood pressure in males and females separately. The results, as in most other studies (108, 197, 226, 227, 229, 230, 241-243) suggest that the risk of stroke death is significantly and independently related to the level of antecedent blood pressure. The risk of increased stroke mortality appeared to be related even to a single blood pressure determination made during the initial health examination, despite the effect of lability, diurnal variation, artifacts of measurements (obese arm, technical errors, digit preference and other sources of variation (237)) and the response to therapy (108).

The standardized normal deviates, calculated according to the Whitehall Criteria (120), provide an estimate of the capacity of each component of the blood pressure to predict those who were at high risk of stroke death in the total population under study. On the whole, there was no significant difference in predictors of stroke mortality between DBP and SBP, MAP or MAI for both genders and PP in women. Generally, an examination of the mean SND for all blood pressure variables in men reveals a larger deviation for DBP than for SBP, MAI and PP. MAP and MAI did not predict stroke deaths any better than the DBP, although they were generally better than the SBP or PP. The observation that MAP and DBP and MAI and SBP as single measures predict stroke mortality to the same extent may derive from the fact that MAP and MAI are combinations of both SBP and DBP and reflect the effect of DBP and SBP respectively. There is nothing to suggest that MAP is better predictor than MAI in both genders. It is also

consistent with the hypothesis that both components of the blood pressure are not making a greater contribution than either alone.

Univariate analyses of mortality from stroke, in the upper quintile of SBP and DBP also favoured SBP as predictor for males and DBP for females.

Multivariate analyses indicate that in females, when SBP and DBP are analysed either separately or together, DBP was found to be a stronger predictor of stroke mortality than SBP. In males, when SBP and DBP analysed separately and simultaneously the SBP and DBP showed essentially the same predictive accuracy for stroke.

Another way to examine the possibility that both components of the arterial pressure contribute independently to risk is to determine if prediction of stroke mortality is better achieved by employing a combination of both SBP and DBP values rather than either alone. The MLR analysis revealed that in males both MAP and MAI are better predictors than SBP or DBP alone; there was no significant difference between MAP and MAI. In women, MAP and MAI were not better than DBP alone but achieved more than SBP alone, and MAP achieved more than MAI.

In conclusion, DBP predicts stroke death more strongly than SBP for women, while in men SBP and DBP predict stroke mortality to the same extent. In men MAP and MAI may be better predictors than either SBP or DBP alone, while in women, DBP alone was a better predictor than any other combination of SBP and DBP.

CHAPTER 12

COMMUNITY HEALTH INDEX AND GENERAL PRACTITIONER RECORD LINKAGE FOR COHORT FOLLOW-UP PURPOSES

SUMMARY: Medical record linkage provides a powerful tool for investigators in a variety of health related disciplines, in particular, extensive use of morbidity and mortality record linkage is made by epidemiologists conducting studies of the incidence and prevalence of disease, disease aetiology, treatment effects, health service evaluation and adverse effects of drugs. The use of medical record linkage for epidemiological investigations offers many advantages: it allows a relatively large number of cases to be followed, relatively inexpensively and provides the opportunity for longitudinal studies. However, for a record to be used as a valid tool in epidemiological studies, it is essential that it contain data of high quality as well as completeness and validity.

The development of the feasibility of following-up a cohort through record linkage using the Midspan registry, CHI and GP records is described. The follow-up methodology used in contacting 981 residents and their GPs in a urban community in the west of Scotland is presented. They were sampled from the upper, middle and lower 5% of blood glucose distribution. The current address of patients can be found by using the name, gender and date of birth from the Midspan file and searching the computer-based CHI of Argyll and Clyde Health board. Attempts were made to contact 937 matched individuals, identified in this way, who were asked to complete a questionnaire about their current diabetes status. Thirty two (3.4%) individuals had moved to other health board areas, 65 (6.9%) could not be traced, and 97 (10.3%) did not reply. the follow-up response to three sets of mailings totalled 80%. The availability of this system makes such large scale studies feasible and economical.

CONTENTS

CHAPTER 12

12.1. INTRODUCTION

The long-term follow-up of community based populations poses unique problems. These problems include declining response rates at re-examinations, the cost and time needed to conduct re-examination on large populations and the accuracy and completeness of data. In the epidemiological investigation of chronic diseases, putative risk factors may precede disease onset by many years, and long-term follow-up of study subjects is essential. Since no statistical technique can adequately correct for the effect of non-respondents on study results, it is important to contact as many subjects as possible (250-252). In today's highly mobile society, this can be a difficult task. To overcome this problem and to ensure as complete coverage as possible for the protracted period of years needed to observe the development of new disease in those originally healthy, follow-up has been by an indirect method of surveillance called medical record linkage.

Follow-up methods for persons with disease, for occupational groups, and for school alumni have been described (253-255). Individuals with disease may be easily located when they have been identified in public health records, such as disease registries. Company records and alumni offices can often provide recent address information for contacting study subjects. However, many population based studies recruit total communities, consisting primarily of asymptomatic

participants, for long term follow-up. The Framingham study of cardiovascular disease in the United States of America (257) and others (1-14) are examples of such studies. This study describe the methodology used in follow-up of another community based population study in the west of Scotland.

Today record linkage is accepted as a necessary tool for epidemiological research and the term is in general use, particularly in the detection of associations between variables or exposures and outcomes of interest. Especially in chronic disease epidemiology, no single record made in one place at one time can describe the evolution of disease (258). Assuming that the routine record systems exist, upon which record linkage may be based, periods of follow-up can be extended for as long as desired; record linkage may be the only method suitable for the detection of new chronic events which take many years to develop. The Scottish Morbidity and mortality Record system is amongst the most advanced in Europe. A great deal of information is collected on many aspects of health related disciplines, and while used primarily for manpower and resource planning, it provides a valuable resource for epidemiological research.

Medical record linkage involves assembling several records into a meaningfull array. Records of illness, treatments, immunisations, delivery, birth and death are made routinely in the course of medical practice. Normally, these are dispersed among records departments of the agencies that initiated them. Outcomes in cohort studies can be validly assessed by using computerised

record linkage techniques to improve the completeness of follow-up and to economise in resources, but there are methodological problems which vary between different type of linkage.

While record linkage provides an excellent mechanism for epidemiological studies, it usefulness is governed by the quality as well as quantity of recorded data. The objectives of this chapter are to describe the concept of medical record linkage in terms of definitions, types, uses, methods and problems and to present the feasibility of linking the CHI and GP's records for follow-up cohort studies.

12.2.THE CONCEPT OF RECORD LINKAGE

12.2.1.Definition: A number of definitions have been suggested for the term "record linkage". One dictionary (259) defines "record" as "an account of an event or piece of information which is kept in writing or some other forms so that it is available for people to refer to" and "linkage is the act or process of joining two things or ideas so that they become connected in someway". The term record linkage was first used by Dunn (260) in 1946 to denote a comprehensive approach to linking events of significance for health. In the words of a speech by Dunn: "each person in the world creates a book of life. This book starts with birth and ends with death. Its pages are made up of the records of the principal events in life. Record linkage is the name given to the process of assembling the pages of this book into a volume". Acheson (258) in his book on medical record linkage defined it as

" a system of linked health records which bring together selected data of biological interest for a whole population commencing with conception and ending in death, in a series of personal community files, the files being organized so that they can be assembled in family groups. The term record linkage may apply specially to the techniques of assembling the files in spite of errors and omissions in the identifying particulars, or may be used in a more general sense to apply to the organization involved". Newcombe (261) defined record linkage as the bringing together of separately recorded data relating to an individual or family in spite of discrepancies or omissions in the identifying particular. Skegg (262) defined record linkage as method of systematic linkage of records about every individual in a large population. Finally, record linkage refers to the method of bringing together information about a single individual or family from different records. This can be done ad hoc in the execution of a research project, or systematically for whole population. Although there are differences in emphasis and wording there is also much in common.

12.2.2.Type: Over a long period, records of several episodes of illness or similar "events" may be linked together to form a person's medical history.

Records relating to individuals may be linked or assembled into groups of particular interest. Record linkage can be classified according to the use which is to be made. These include: 1) treatment effect 2) adverse effect of drugs 3) health service evaluation 4) aetiology of disease 5) natural history of diseases 6) morbidity and

mortality following therapeutic trials 7) maternal and child health 8) associations between diseases and 9) monitoring for occupational hazards.

Rather than approaching record linkage classification by use, it is possible to classify record linkage by the sources of data. There are nine type of sources for medical record linkage that it is possible to link within or between them. 1) hospital records 2) NHSCR 3) patient registries 4) population-based study 5) school entrant and leaver medical examination records 6) CHI 7) the Prescription Pricing Authority 8) census and 9) GP records. The characteristics of each of these types are as follow:

1) Hospital discharge summaries in Scotland (SMR data) are recorded, collected and collated by hospitals and the Information Service Division (ISD) of the Scottish Health Service Common Services Agency. They include: (a) General hospital discharge records (b) obstetric hospital discharge records (c) mental and mental deficiency hospital admission and discharge. Another source of data used in hospital care and recently computerized is Master Patient Index (MPI) (263).

2) NHSCR is a central record of all NHS patients registered in Scotland. It includes records of births, deaths and stillbirths and information on immigration, emigration, and other items. Its chief function is to ensure complete and accurate data on every individual registered with a GP, updates for death and, where known, emigration. In addition it has the purpose of facilitating the payment of GP on the basis of a

capitation fee for each patient registered. Recently, NHSCR has participated in the National Cancer Register scheme organised centrally by ISD. In Scotland, the GRO has been responsible for the registration of vital events, but copies of each draft entry of birth and death are also sent to the NHSCR at Ladywell House in Edinburgh.

3) patient registries include different chronic and infectious diseases such as thyroid (264), cancer (258, 265), handicapped children (258, 266), blindness (258, 267), mental illness (258, 268), rheumatic fever (269), burns (270), heart disease (271), child abuse (272), trauma (273). The use of disease registers provides one method of record linkage for the study of chronic disease. The widespread availability of computers has contributed to this trend but the difficulties of maintaining a high standard of completeness and reliability of registers' data are well described (274).

4) population-based studies are an important method of follow-up in epidemiological investigations through linkage with morbidity and mortality records.

5) school entrant and leaver medical examination records include a medical record of all children who enter school; this has been computerized since 1967 in Scotland.

6) a CHI is a central record at health board level of basic information such as name, address and GP details for every individual registered with a GP.

7) The Prescription Pricing Authority is a centre for the pricing of prescriptions written in general practice. Prescriptions written by GPs always have a GP's name and

address stamped on them, and identification of the recipient becomes much easier if the data on the prescription can be compared with a list of the name, address and age of the patients in the practice concerned or CHI file.

8) Much data of value to medical research workers are included in the census such as information about occupation and industry, birth place, migration and higher education, which if linked with mortality and morbidity data would be of considerable research value. The data recorded about each individual includes full personal identification. The GRO is bound by law to disclose no data about an identifiable person to any other person or to a government department (258).

9) GP records are another important source of data for epidemiological research purposes. Everyone in the U.K. has a personal doctor and the GP is responsible for recording in writing most of the important health events which his patient experiences in the home, out-patient clinic or hospital. The basic clinical records also contain full name, address, date of birth and NHS number. Furthermore, at least in theory, these records should follow the patient as he moves about the country. A GP's record should thus provide a summary of the cumulative health record of the individual including immunisation, accounts of important diagnosis, operations, consultant opinions, treatment and of drug idiosyncrasies.

12.2.3.Use: Medical record linkage systems have been used for a wide variety of purposes. Roughly, first to ascertain the relationship between separately recorded

events occurring to the same individual in different places and at different times (personal linkage); second to ascertain relationships between individuals which may be associated with their health or illness (family linkage).

So far, seven main areas of application have yielded important results (275):

1) **Identification of individuals** -to provide the GP with access to a large number of individuals with a particular condition.

2) **Epidemiology of chronic diseases**- (a) to provide a basis for estimating incidence and prevalence rates for a defined population; (b) to permit the natural history of a condition to be followed; (c) to attempt to identify aetiology and outcome of treatment and (d) association between diseases.

3) **Preventive medicine** -screening and identification of high risk groups, vaccination and immunisation, follow-up surveillance.

4) **Planning, operation and evaluation of service** -to make it possible to estimate the need for services and to evaluate programme efficiency and effectiveness, readmission patterns, mortality and morbidity follow-up operations, and models of health service function.

5) **Evaluation of treatment** -to provide the basis for calculating the efficacy of various therapeutic techniques.

6) **Genetic** - congenital anomalies and their relationship to birth order and birth spacing.

7) **Social psychiatry** -social mobility, parental loss,

birth order and subsequent, emotional illness in married couples.

12.2.4.Method: There are two forms of record linkage (275):

1) All-or-none linkage by means of a single, universally available, completely reliable and checkable identifying characteristic. This is simple, economic and reliable and when it can be applied is the best method to use. The identification characteristics usually take the form of a unique number. In some countries (e.g. U.K. and Scandinavian countries), such a number has been assigned to every member of the population, usually at birth. They are often at least partially made up from stable features of the individuals such as date of birth, gender and so can be reconstructed if lost.

In the U.K., the NHS number is virtually such a unique number. Unfortunately, it is not always available, it takes various and often complex forms, it is not quite unique, it is not completely reliable, and it is extremely difficult to check automatically. Nevertheless, it is the chief identifier in the NHSCR, and a feasibility study for a national medical record linkage system recommended its use.

The advantage of a unique number system is that the actual linking procedure is easy. The disadvantage is that if the number is not accurately recorded, or not available, non-unique characteristics such as name must be used in a clerical procedure to obtain the number. If the proportion of errors or missing numbers is high, the

special advantages of all-or-none linkage are lost. There are circumstances in which the conditions for all-or-none linkage can be met. These occur wherever prenumbered documentation is practical, as for instance, in some types of clinical or administrative records.

2) Probability linkage, based on a group of characteristics of varying availability, stability and discriminating power. Identification of patients usually depends on such information as gender, first name, surname, address and date of birth. A decision as to whether two documents bearing closely similar sets of these items refer to the same person clearly must be based on some assessment of probability.

With small files of only a few thousand names as in a general practice, the probability of a correct match is very high. However, in a larger files, the chances are greater of data sets occurring which are almost identical, but which refer to different people. Nearly all name indexes in hospital medical records systems, which may contain records of hundreds of thousands of people, are based on simple identification.

The advantages of probability linkage derive from its use of a computerised medical database which provides convenient, quick and cheap follow-up data. The disadvantage of this method is the failure to link records which should be linked and linking records which should not be linked.

It has been shown that even in small indexes of a few tens of thousands of records, accuracy in clerical matching is closely related to the amount and quality of

the identifying information. Missed and false-positive linkages can be virtually eliminated if a fuller identifying data set is used.

12.2.5. Problems: While medical record linkage may serve a wide variety of uses, there are many problems associated with its establishment and maintenance. Foremost among these are confidentiality, matching, completeness and accuracy. The technical problems of matching mentioned in previous sections, confidentiality, completeness, accuracy of morbidity and mortality data and validity of technique will be discussed.

Any form of record linkage will involve serious security and confidentiality risks unless considerable care is taken in the design and operation of the system. We must be specially careful to establish adequate safeguards of individual privacy and identity so that there will be little possibility that data available for any linkage system will be misused. An individual's right to privacy must be balanced against the valuable knowledge that can be learned from a computer-based system that includes information on every medical encounter, illness and use of resources. The potential threat of a linked database, to individual privacy, is likely to increase as computer power increases. Record linkage, in the absence of a unique identifying number, based on multiple individual characteristics is becoming increasingly practical. Given this new power to identify individuals and their activities, independent of the use of a unique identifying number, careful control of access to

information that allows identification of specific individuals in a database would seem our strongest safeguard against abuse of this information. Confidentiality can be achieved by restricting access to computer records to authorized personnel, perhaps by keeping such records free of names and addresses, if clerical records exist they could be stored in a separate place and by keeping the files of the matched data separate from the original file. In Scotland, adequate safeguards for the individual appear to exist (276, 277), and there is no evidence of abuses of this powerful database yet. With this linked record system, Scotland has a significant tool to help in providing care for its countrymen and to monitor its society's health.

One of the problems with which all medical record linkage must deal is the quality of medical record data. A potentially more serious limitation of this system is its reliance on the accuracy of coding of discharge diagnoses. Although a study by Lockwood (278) found the coding accurate for 94% of the diagnosis and Martini et al. (279) found greater than 90% of recorded principal diagnoses were correct, others have claimed that higher levels of error may occur (280, 281). A study by Coid (282) for assessment of stroke hospital diagnosis found accuracy of 95%. Recently Heliovaara et al. (283) reported that although hospital discharge information under-estimates morbidity in the population, the data are sufficiently valid for many epidemiological purposes. The diagnostic accuracy of hospital records was satisfactory.

Mortality data and statements of causes of death on

death certificates continue to be used as the major source of information characterizing the health of the population and are frequently used in linkage record systems. However comparison of death certificates with clinical and autopsy records has led to the conclusion that mortality statistics based on cause of death are of dubious accuracy. Alderson and Meade (284) in comparing 1,216 deaths and the hospital records of the patients, found 39% discrepancies in recorded causes of death using two digit ICD code accuracy. Beadenkopf et al. (285) studied matched autopsy protocols and death certificates and found a low specificity and sensitivity for CVD and high concordance for malignant neoplasms. Britton (286) reported that 57% of causes recorded on death certificates agreed with the autopsy diagnosis in a series of 400 cases. Dorn and Cutler (287) studied the death certificate and case reports for 22,681 deaths with neoplasm recorded as cause and found significant misclassification in the death record, particularly for malignant neoplasm of cervix and uterine corpus. Fedrick and Butler (288) in a comparison of cause of death coded in the British Perinatal Mortality Survey and in the GRO, on the same records, found major discrepancies in the two records, the implication being that coding errors constitute an important problem. Gwynne (289) reported 58% of death certificates were in error when compared with autopsy findings.

Heasman and Lipworth (290) reported that in a major study of 9,501 autopsied deaths occurring in 75 hospitals in England and Wales, a new death certificate was

completed by the clinician without reference to the autopsy finding and a second by a pathologist. The certificates were coded independently in the GRO and the two underlying cause codes compared. In only 45% of the records was there complete agreement. James et al. (291) in a study of 1,889 death certificates and matching autopsy records, found 52% agreement using three digit and 71% using two digits of the ICD. Paton (292) reported on a series of 414 cases with post-mortem examination, found 118 with acute myocardial infarction (AMI) both pre and post-mortem, 96 with clinical diagnosis of AMI but no autopsy confirmation. This amounts to a false positive rate of 45% and false negative rate of 31% using the autopsy finding as definitive. Numbers of additional reports comment on the inaccuracy of death certificate reporting of lung cancer (293, 294), cerebrovascular disease (295-297), pulmonary embolism (298), paediatric CVD (299), tuberculosis (300), suicide (301-303), pulmonary infarction and embolism (304, 305), Chronic respiratory disease (306), uterine cancer (307) and pericarditis (308). A review of the literature by Gittelsohn and Senning (309) on the accuracy of cause of death certification documents that major problems exist in the quality of the information being collected, coded, and tabulated.

The central issue underlying the problem of validity of cause of death is the reliability of the diagnostic process itself.

However, since many theories and even expensive research project are established on the basis of

statistical findings of medical record linkage, it is important that the quality of records being used should be as high as possible.

12.3.EVALUATION OF MEDICAL RECORD LINKAGE

Two fundamental concerns should govern the evaluation of medical record linkage data: completeness and validity. The completeness of data is defined as the proportion of all cases in the target population which appear in the medical record database. If a record is population based, such as NHSCR and ISD, then all cases of death or diagnosed disease for a defined population theoretically appear in it. For hospital in-patient records, all cases of disease seen at the reporting source should be included. If completeness is not guaranteed, it is necessary to identify those factors which are related to the selectivity of case inclusion. The results of systematic bias in case reporting is the calculation of misleading rates of disease. For example, if a record is 60% complete and the data which are missing come from a random group of cases, the extent of disease will be under estimated, but the underestimation will be the same for all patient subgroups. However, if the missing data are concentrated on one case characteristic (for instance, the least severe case), the error in the calculation of rates would be compound; the extent of the disease would be underestimated as before but, in addition, the relative frequency of severe cases would be overestimated.

Validity is the second essential component in assessing the quality of medical record data. In this

context validity may be defined as the proportion of cases in one record which "truely" has been matched with the other record. In practice, it is the proportion of agreement between two recorded sets of data. The need for recorded data with a high degree of validity is obvious; case ascertainment may be nearly complete, but the record may contain a high proportion of information which is incorrect. Once again, the importance of differentiating between random errors and systematic errors must be stressed. The critical test of effectiveness of any linkage system is the sensitivity and specificity of the procedure in identifying correctly the cohort having subsequent events. Hole et al. (310) considered this aspect of the method and found levels of sensitivity of 66% for mortality and 81% for the inpatient data based on the probability linkage method.

12.4.USE OF CHI FOR FOLLOW-UP PURPOSES

The objective of medical record linkage system is to provide an economical system for collecting morbidity and mortality events based on routine statistics. One of the additional objectives of the Scottish medical record linkage is to provide a means whereby individuals can be followed up for clinical and epidemiological purposes (266). The record linkage through Scottish Hospital In-patient statistics produces details of diagnosis and outcome on hospital admission and, through the Registrar General's mortality records, produces information about death. As mentioned earlier the quality of computerized databases, may not always fulfil the criteria of validity. However, all of the previous record linkage studies are

limited to hospital in-patient events or mortality outcome, and so will only be able to detect events causing hospitalization or death. But how can we follow patients whose outcome of interest generally will not result in hospital admission or death, with an acceptable response rate? The only known reliable way of follow-up is to repeat examination of the subjects, but the problem involved in maintaining contact with patients increases with time after their baseline examination. The repeat examination of individuals has the advantages that the data collected are accurate and relevant for scientific purposes, but high cost and feasibility problems may prohibit this choice. One way to tackle this problem is record linkage with available registers maintained for other purposes to have access to subjects and their health records. CHI is one of these registers. With linkage to CHI it is possible to have access to the last known address of patients as well as his/her GP's name and address and finally can have an access to them as well as their GP's record.

12.5.SAMPLING AND METHOD

This study describes the existing and potential uses of the CHI.

There is less experience to date in the use of the CHI and GPs' records for epidemiological follow-up studies than in the corresponding use of the mortality and hospital admission databases.

In this chapter, methodological problems regarding this linkage will be discussed. Also discussed are the

results of a preliminary linkage of the two data files to provide a basic facility to follow-up a population based cohort for non-hospitalization events and decrease the degree of losses to follow-up due to changes of address.

We were required to link a sample of the Paisley file with the CHI to find the last known address of the subjects and their GPs and follow this up by a mail questionnaire and reference to GP practice records, to determine the validity and practicability of the method, as well as to determine the trends and outcome of asymptomatic hyperglycaemic subjects, as defined in next chapters (Chapter 13).

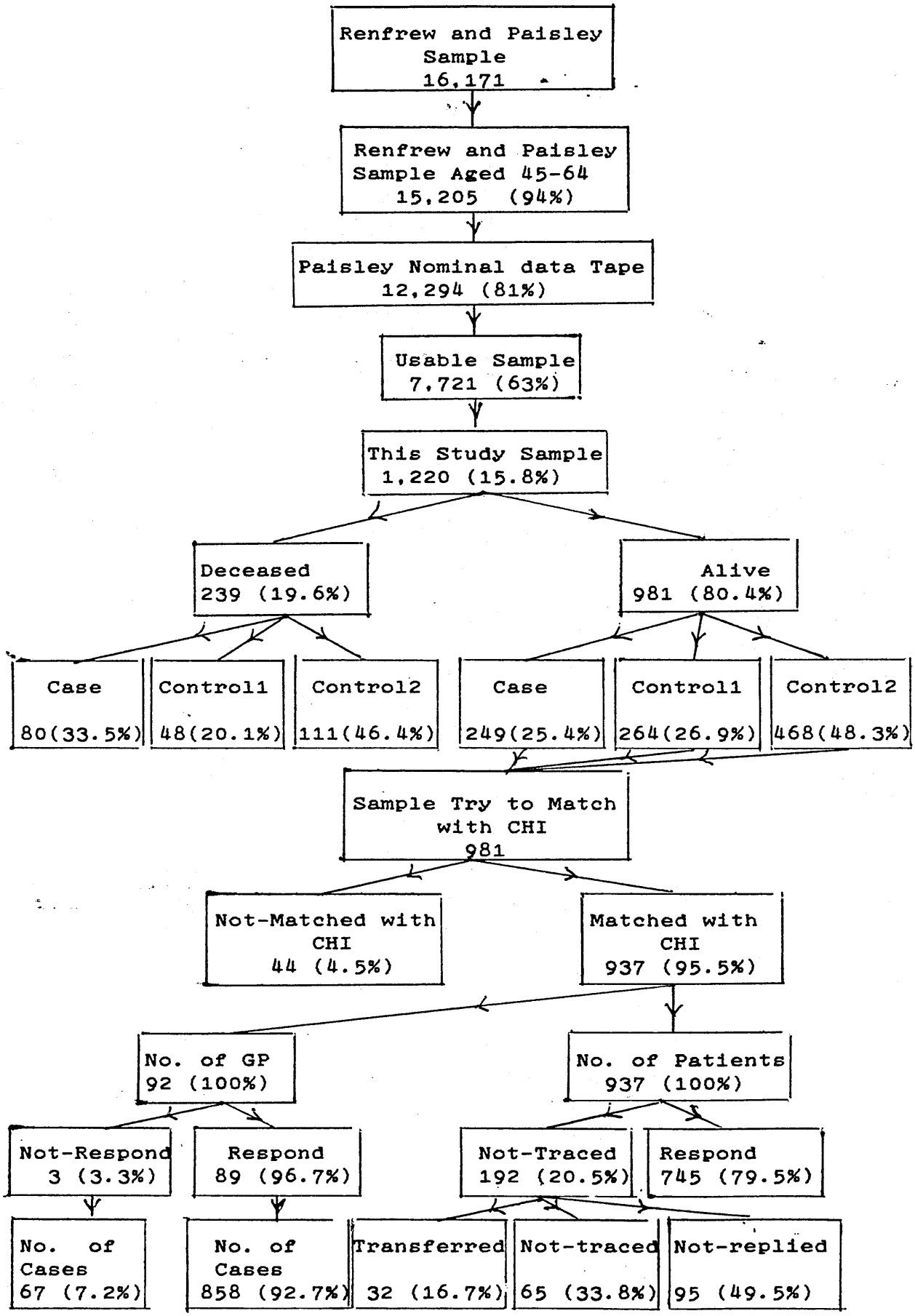
12.5.1.Study Subjects

The follow-up survey was conducted as part of the Renfrew and Paisley study between October 1987 and April 1988. The purpose of the survey was to determine the diabetes status of subjects who had participated in the first phase of the Renfrew and Paisley survey, 10-14 years earlier. The study cohort was a sample of 981 residents from the original study population consisting of 7,721 men and women aged 45-64 years, all with blood glucose measurement in 1974-76 in Paisley. The follow-up procedure demonstrated in the following flow chart (page 220). They had participated in only two phases of the Renfrew and Paisley study 12-14 and 9 years earlier and had not been contacted since. This study is "flagged" with the NHSCR to report mortality outcome monthly. The surname, first name, title, address and mass miniature radiography number (MMR) of each examinee was recorded on magnetic computer tape at baseline. Using NHSCR or any other register to follow-up

patients may however involve ethical problems (311). Each member of the cohort gave written permission for his or her medical record to be examined by the study team for research purposes. Written permission was also obtained from GP Sub-committee of Argyll and Clyde Health Board Area to write to GPs and to patients in the identified subgroup. Once records were linked, particular care was taken to safeguard confidentiality.

The sample selection was based on upper, lower and middle 5% of Renfrew and Paisley blood sugar distribution. After the sample selection had been carried out it was found that the computer magnetic tape of names and addresses belonging to Renfrew study was lost. Thus, we decided to consider only the Paisley sample.

The sample comprised 249 cases with asymptomatic hyperglycaemia (defined as casual blood glucose $\geq$126 mg/dl at baseline). Two control groups have been selected from the lowest (468) and middle (264) parts of the glucose distribution, to minimize the probability of overlapping. The 239 (19.6%) individuals who had died before April 1st, 1988 and reported by NHSCR, or found during the matching procedure with CHI and who were known to be diabetic at baseline were excluded.


Renfrew and Paisley Sample 16,171
Renfrew and Paisley Sample Aged 45-64 15,205 (94%)
Paisley Nominal data Tape 12,294 (81%)
Usable Sample 7,721 (63%)
This Study Sample 1,220 (15.8%)
Deceased 239 (19.6%)
Alive 981 (80.4%)
Case 80(33.5%)
Control1 48(20.1%)
Control2 111(46.4%)
Case 249(25.4%)
Control1 264(26.9%)
Control2 468(48.3%)
Sample Try to Match with CHI 981
Not-Matched with CHI 44 (4.5%)
Matched with CHI 937 (95.5%)
No. of GP 92 (100%)
No. of Patients 937 (100%)
Not-Respond 3 (3.3%)
Respond 89 (96.7%)
Not-Traced 192 (20.5%)
Respond 745 (79.5%)
No. of Cases 67 (7.2%)
No. of Cases 858 (92.7%)
Transferred 32 (16.7%)
Not-traced 65 (33.8%)
Not-replied 95 (49.5%)

12.5.2.Community Health Index

One set of collected data at health board level in Scotland is a CHI file. A CHI is a list of people who are eligible for health services and will usually store the name, gender, date of birth, address, marital status, GP's name and address, date of registration with the practice, date of removal, NHS number and CHI number. These data are computerized and processed by the Argyll and Clyde Health Board Area. The health board also provide an alphabetical listing of these patients on microfiche. A computer system was introduced for CHI in 1977. The coverage of the scheme has improved since its inception and from 1980, CHI has been available for 100% of the people resident in Argyll and Clyde Health Board Area and registered with a GP. However the facility exist in the CHI computer system to trace patients by combination of name, date of birth and gender.

One of the advantages of CHI for the conduct of follow-up cohort studies is that every person registered with a GP has been allocated a unique number, the so called Community Health Number. This number provides the method of identification and access to a separate computer file which contain patient biographical details, details of all hospital discharges, death notifications and also child development records (312).

12.5.3.Study Sample and CHI Linkage Method

The linkage method employed was an on-line inquiry facility provided by Argyll and Clyde Health Board, which allows searching date of birth and gender and then first name, surname and address matched visually. For those

people whose surname and first name could not be found using date of birth and gender a search was made of an surname alphabetic microfiche. A listing can then be produced of all pairings. The surname, first name, address and date of birth of a selected sample was extracted from a separate magnetic computer tape prepared at baseline examination based on MMR.

The last known addresses and GP's name and address of those who was needed for follow were identified by this matching procedure.

Individuals were contacted by mail and the accuracy of responses was checked by referring to the GP's records.

Contact by Mail: Survey questionnaires were mailed to a selected sample and asked to check name, date of birth, address and GP's name and address, and if it was not correct write in the correction. Subjects who did not respond were sent two reminder with about one month interval between them. Mailings consisted of an introductory letter, a questionnaire and a pre-paid self-addressed return envelope. The GP records were then searched by writing to the GP to validate the accuracy of the responses from the postal questionnaire. The information gathered from patients was sent to the relevant GP who was asked to check the accuracy of information and if it was wrong write the correction. This study population consisted of people registered with 100 GPs in 56 practices. The practices were mainly in the Renfrewshire area and comprised 74 group practices and 26 solo practices. Eight GPs were outside Renfrewshire and

excluded.

The validity of the study results depends on the accuracy of the linkage process. To test this accuracy, records of 981 individuals of the cohort study were matched with the CHI file. The validation first involved a search for incorrect matches. A three stage method was used, firstly, the surname, first name, date of birth, gender and address on the CHI were matched with the cohort file and if the first four items were the same but not the address then the address of the CHI was taken to be the correct one. Secondly, those items were confirmed by the patients. Thirdly, GP were also asked to confirm the details.

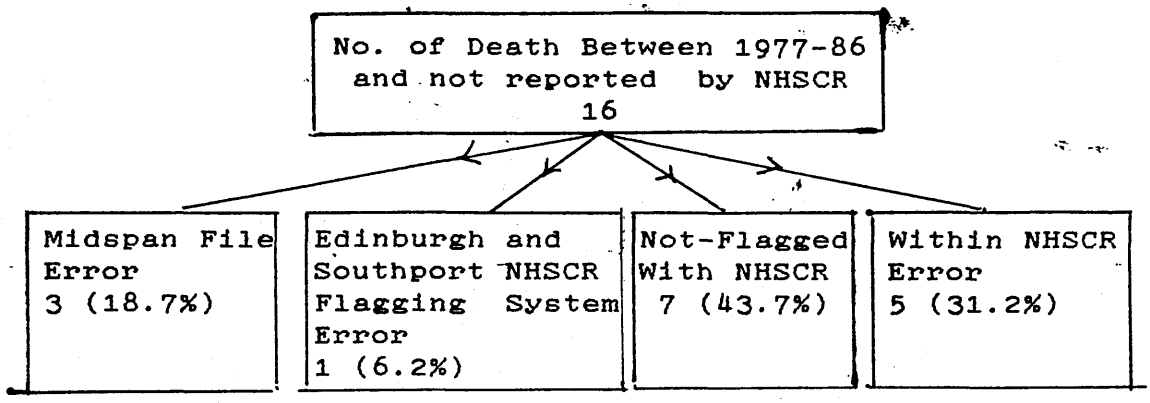
Contact by Telephone: When mailings were finished, 192 (20.5%) of the 937 men and women in the target population remained to be contacted. Thirty two (32%) of them were transferred to another health board area and 65 (33.8%) could not traced by mail and 95 (49.5%) did not respond. However, all of the not-traced and non-respondent subjects were found through GP's records. Eleven (12%) of 92 GPs after two mailings also remained to be contacted. However after telephone contact 8 GPs responded, further improving the response rate of GPs from 88% to the final 96.7%. Three GPs have not been contacted anymore, one of them refused to participate and two others did not send back the questionnaires.

At the completion of the survey, all baseline participants were contacted through mailing or GP records.

12.5.6. Linkage with National Health Service Central Registry

The Renfrew and Paisley subjects were "flagged" with NHSCR. Flagging is a process by which all individuals in the study are identified in the NHSCR file of the Scottish population, so that the occurrence of death in a person previously notified to the NHSCR can be made known to investigators (313). Of the 16,171 subjects examined at baseline, 2,797 were known to have died by 1 January 1986. The correctness and completeness of mortality flagging were established by comparison with death reported as a result of manual tagging of the study cohort in the NHSCR. In a test sample of 981 persons who thought to be alive at 1 January 1986, we found 16 example of failure to notify a death. These 16 cases were followed through the Registry, as shown in following flow-chart. Three (18.7%) cases were flagged and notified to Midspan file but they were not transferred to computer file. One (6.2%) of the cases died in England and flagged at Southport but not reported to the Scottish NHSCR. Seven (43.7%) cases were not flagged with NHSCR at baseline. Five (31.2%) cases were flagged but their deaths were not reported to Midspan by NHSCR. Of 16 errors, there were 5 (31.2%) errors in NHSCR (4 human errors and 1 system error), 1 (6.2%) system error between Southport and Edinburgh NHSCR, and 7 (43.7%) errors in flagging and 3 (18.7%) errors within the Midspan file.

The NHSCR also provide copies of each certificate and of the coding of the cause of death according to the Ninth Revision of the International Classification of Disease.



12.6. RESULTS

Of 981 individuals matched with CHI, 44 (4.5%) failed to match due to minor differences in the names and mistake in date of birth.

Table 12.1 presents the number of linked records. Of the 981 Paisley file records sample which could possibly be linked, 870 (88.7%) were linked to CHI records by matching on all four items by computer alone. A further 67 (6.8%) matched on microfiche giving an overall linkage of 95.5% of the Paisley sample file. Table 12.2 shows the final figure for the survey population. Out of 937 matched pairs 62 (6.3%) had died, 16 (1.6%) subjects died before January 1st, 1986 and 42 (4.3%) individuals died after 1986. Of matched individuals 192 (20.5%) could not be traced through mail using the identification information obtained from the CHI and Paisley records. The commonest cause of failure to find them was incorrect or changed address, or transfer to another health board area. 32 (16.7%) of people could not be traced by mail and were identified by CHI file to have transferred to another health board area, 65 (33.8%) could not be traced and 95

(49.5%) did not reply. There were 350 (35.5%) subjects who had changed their address since baseline examination.

The 937 subjects matched correctly and who were alive were followed through postal questionnaires. Table 12.3 shows the mailing response rate by individuals. The questionnaire from the first mailing were returned by 589 (62.9%). An additional 118 (33.9%) of non-respondents responded to the second mailing, and increased the response rate to 75.4% (707). Then a second reminder was issued and 38 (16.5%) of non-respondents responded to the second remainder or third mailing and the final response rate became 79.5%. 745 individuals were successfully contacted. When mailings were finished, 97 (10.3%) of questionnaires had been returned by the post office stamped " gone away, no answer, not known at number". The remaining 95 (10.1%) subjects had apparently received mailings but had not responded. The non-traced status was checked by CHI again and 32 (16.7%) of subjects were found to have transferred to another health board. The non-respondents status checked by GPs and all of the subjects found in GP records.

There was 100% agreement between the Paisley file, CHI and patients concerning first name and surname. Only in one case was disagreement found between CHI and a patient regarding date of birth. About 10 cases moved within health board area and their new addresses were not found in the CHI file, and 11 cases moved from the health board area were successfully contacted. The major disagreement between CHI file and patients was over GP's

name. There were 105 (11.2%) cases that patients claimed their GP's name to be wrong but both patients and CHI file agree that they are within the same practice. However patients registered with one GP often attended other GPs in the same practice. Thirty seven cases claimed that their GP address was not correct. All of these cases were within a big practice which recently moved to new premises. Two cases refused to give permission to have access to their medical records and 2 cases did not like to participate anymore in the study due to ill-health.

12.6.1.Mortality: Linkage of a sample of 135 reported deaths in the cohort during 1974 to 1986 with the CHI generated 98 (72.6%) matches. Only three non-matches died after 1979 and 34 cases before 1979. 27.4% of the deaths were not matched with the CHI file, 25.4% of them died before 1979 and this is expected because they occurred before complete implementation of the CHI file.

12.7.DISCUSSION

By using existing information which has been gathered in an independent record system, record linkage can create a composite history at considerably lower cost and time than would be necessary to follow a cohort of subjects through years of vital events and encounters with public health services. Record linkage has many potential application to following cohorts to detect a new disease in a well population, as well as in evaluating health services, treatment effects and side effects of drugs without physical re-examination. In this study, for the first time the description of methodology for assessing the feasibility and practicability of follow-up of a

cohort through linkage between GP's records, CHI file and the cohort file was considered. The actual results of determinating of trends and outcome of asymptomatic hyperglycaemic subjects will be discussed in the next chapter.

However, CHI can be used to acquire information about the movement of patients from one area health board to another but cannot assign either the name of the new area health board to transferred patients, nor the new address and name of the GP. This difficulty of maintaining contact with certain groups of patients who moved to another health board area has been accentuated by the recent increasing mobility of populations in Scottish towns and cities. Patients may be lost to follow up in this way so, if all area health board after computerization are linked to each other by a NHSCR, then these transferred patients could be followed-up. However as Hedley et al. (311) stated, if patients are registered with a new practitioner, then contact may be reestablished through that GP unit providing that the patient's entry in the NHSCR can be located. In this study attempts were made to contact 937 individuals identified by the CHI, who were asked to complete a questionnaire about their current diabetes status. Of the matched individual 20.5% (192) could not be traced through the mail. 3.4% were due to transfer to another health board area, 6.9% could not traced and 10.3% did not respond. Not-traced rate is considerably lower than the findings of Jones et al. (314) of 18% based on the information collected by the Prescription Pricing Authority, clinic records or GP records.

However, in this study, all of the not-traced individuals were identified through GP's record linkage.

The speed, accuracy and response rate of follow-up could increase if it were possible to link the CHI file with a computer file of a telephone directory to identify telephone numbers of non-respondents and contact them by telephone. This is possible in countries such as France where the directory is available to any subscriber possessing a Minitel computer terminal.

Availability of CHI and GP records as a facility for cohort follow-up studies is too recent to have provided much experience in its use, but the CHI file and hospital in-patient statistics, as well as mortality statistics linkage have been actively employed for sometime and the demands for its use are increasing (262).

The existence of CHI record linkage in the Argyll and Clyde Health Board Area offers the potential for follow-up Midspan cohort study through the GP's record. Its use for this purpose compares very favourably, in term of cost and time and ease of procedure, with the alternative of a clinical follow-up study of cohort.

The group of 4.5% individuals unmatched with CHI resulted from differences in the spelling of given names of various types such as letters missing or transposed, and names shortened or anglicized, or from mistakes in typing the date of birth or both, or from women changing their name due to marriage. The chief problem in the searching step arises where the sequencing information (e.g. the surname, first name, and the date of birth) has been stated differently on the two potentially linkable

records (e.g. the surname and first name may be spelled differently, or some part of the birth date may be reported differently on one of the records).

Overall there was a large response to our request. Only 97 (10.3%) of people who we believe were alive and received our request did not respond.

The identification of individuals and access to their health record using CHI and GP records may raise serious questions of confidentiality. Only 2 cases had objections to inspection of their health records by our research team, but the attitude of the 97 (10.3%) who failed to respond to the survey may be important in this respect. Also there are other posibilities -they may have failed to respond to the survey bacause of not receiving the questionnaire, illness, gone away, and death.

In summary, the follow-up of population cohort studies through CHI linkage, and with records of illness seen by GPs in Scotland is far away from perfection but was found to be a practicable method of follow-up.

CHAPTER 13

COHORT FOLLOW-UP USING RECORD LINKAGE TO MEASURE THE ASSOCIATION BETWEEN HIGH CASUAL BLOOD GLUCOSE VALUE AND LATER DEVELOPMENT OF OVERT DIABETES

SUMMARY: The record linkage exercise which enables the feasibility of studying the association between a single casual blood glucose and later development of diabetes has already been described in Chapter 12. This chapter discussed the epidemiological findings and estimates a measure of risk in a cohort consisting of 903 men and women. Information on their diabetes status after a 12-14 year baseline examination was obtained by contacting general practitioners and patients through the CHI.

In the Paisley section of the Midspan study 224 people were in the top 5% of casual blood glucose distribution and non-diabetic compared with 426 individuals in the lowest 5% and 253 in the middle 5% of single initial glucose distribution. Initial casual blood glucose level was related to the development of non-insulin-dependent diabetes mellitus in a maximum of 14 years follow-up, and the data observed were analysed by the life-table and multivariate analysis techniques. Sixteen (14%) men and 12 (13%) women in the index group compared to 5 (3%) men and 3 (1%) women in combined comparison groups worsened to diabetes during this period as estimated by the life table analysis. Overt diabetes was found about 9 times more frequently in men and 15 times more frequently in women for initial casual blood glucose of 126 mg/dl and higher than for those below 70 mg/dl or equal to 90 mg/dl. The prevalence of hypertension and obesity in persons who developed diabetes was greater than in those who did not. A MLR model was used to control the influence of age, gender, SBP, DBP, blood glucose, serum cholesterol, BMI and cigarette smoking simultaneously. Both blood glucose and BMI were significantly predictive of ultimate worsening to diabetes. The frequency of high casual blood glucose level was higher in males than females, but the tendency toward the development of diabetes was more pronounced in females particularly if they were obese.

The study suggested that follow-up of a cohort by means of record linkage with CHI and GP's record would be a useful epidemiological tool for the detection of associations between baseline variables and delayed effects which did not require hospitalization. The findings suggest new opportunities for evaluation in practice of the estimation of a simple risk profile (blood glucose and BMI) in subjects in middle life.

CONTENTS

13.1. INTRODUCTION

Individuals with impaired glucose tolerance have been assumed to have an early phase of diabetes regardless of how blood glucose was measured. However, the possible association between and predictive value of high casual blood glucose (i.e. non-fasting) and progress to diabetes mellitus is not clear. Several studies (315-326) examined the value of different diagnostic criteria for asmptomatic hyperglycaemia and progress to diabetes. None of them used casual blood glucose criteria. In many people, impaired glucose tolerance returns to normal spontaneously, while in some there is progression to gross hyperglycaemia with symptoms. The significance of other factors which influence or predict a state of deterioration are also controversial (350). In this study the question arises as to whether a high casual post-prandial blood glucose level allows a reliable prognosis to be made with respect to the development of overt diabetes. A series of relevant questions may be posed: To what extent does the presence or absence of an arbitrarily defined high single casual blood glucose level play a role in the prediction of diabetes mellitus? How important are BMI, blood pressure, serum cholesterol and cigarette smoking in the prediction of diabetes? Is there any gender difference between the presence of risk factors and later development of diabetes? This chapter attempts to clarify these questions.

In a prospective study of this kind maintaining

contact with patients during a long period of time would be a daunting task unless it could be achieved by linking records collected routinely for other purposes. In Scotland, the CHI is one of these registers. With linkage with the CHI it is possible to have access to the last known address of the patients and the name and address of the GP as well. A feasibility study of the follow-up of a cohort using CHI and GP's records was undertaken (Chapter 12).

This study was undertaken to elucidate the relationship between certain measurements made at baseline and subsequent "progress" to clinical diabetes. The study group consists of 224 cases identified as asymptomatic hyperglycaemics. This was based on casual blood glucose of more than or equal to 126 mg/dl (top 5% of distribution) compared with 679 controls 12-14 years following their participation in the Paisley study by means of a link with the CHI and GP's records.

13.2.ANALYSIS

The population sampling frame and methods of this chapter have been described in detail in section 5 of chapter 12.

To evaluate the relationship between casual blood glucose levels at baseline with 12-14 years and deterioration to diabetes, bivariate analyses were carried out. Continuous variables were dichotomized at arbitrary cut points that could be considered "high"; also the men and women were classified by cigarette smoking at entry to the study, with index and comparison groups. The chi-square and unpaired Student t-test were used to determine the

degree of significance of differences between the groups.

The probability of worsening to diabetes was assessed by application of life-table techniques (327). This actuarial technique, exemplified in Table 13.1, uses observed outcomes for each observation interval for each patient and estimates cumulative proportion which would have been found after all the patients had been followed for the full duration of the study.

13.3.RESULTS

The relationship between initial blood glucose levels and diabetes by age and gender is examined in Table 13.2. At the end of 12-14 years follow-up period 21 (5%) of the 410 men and 15 (3%) of the 493 women had developed diabetes. Of these, 16 (76.2%) men and 12 (80%) women were in the top portion of the glucose distribution, 3 (14.3%) men and 2 (13%) women in middle and 2 (9.5%) men and one (7%) woman in lower portion. Two cases were insulin treated and 34 cases were non-insulin treated. Two cases were diagnosed as diabetes during an initial examination and excluded.

The proportion worsening to diabetes was 14% of men and 11% of women in the index group, 3% of men and 1.3% of women in the mid-range comparison group and 1% of men and 0.4% of women in the lower control group. The proportions in the index group were significantly higher than each of the comparisons. Neither of the comparisons was significantly different. Because of the small number of people who progressed to diabetes in the comparison groups, they were combined for the rest of the analysis.

The life-table projections for cases and controls and for males and females are shown in Figure 13.1. They show that by the 14 years after diagnosis of asymptomatic hyperglycaemia, 13.6% of men and 12.5% of women in the top blood glucose distribution will have progressed to diabetes compared with 3.1% of men and 0.9% of women in the combined lower and middle part of blood glucose distribution.

13.3.1. Influence of Age, Blood Pressure, Body Weight and Gender

Age: Assessment of these results requires information on the comparability of the groups that are under consideration. The age composition is of prime importance since the prevalence of diabetes increases with age. Table 13.3 indicates that both mean ages and the distribution in cases and controls are sufficiently close to avoid any significant effects. In females, but not in males, a higher mean age was observed in those who progressed to the diabetes compared to those who remained unchanged (Table 13.4).

Blood Pressure and Body Weight: In Table 13.4 the mean values of certain baseline characteristics is compared in both the groups who deteriorated and those who did not deteriorate to diabetes". Values from the baseline single casual blood glucose, DBP and BMI were significantly higher amongst those who deteriorated to diabetes in both genders, and age and SBP in females. According to Bonferroni's inequality (328) when K tests are performed, each with significance level P, the probability of one or more significance tests by chance

alone is at most KP. When we applied this coefficient, DBP in both genders and BMI in males were no longer significant.

Variables were dichotomized to further analyse the effect of being overweight, hypertensive, having a high serum cholesterol or being a smoker compared with being "normal" in relation to progress to diabetes. In Table 13.5 incidence rates and relative risks are given for individuals worsening to diabetes in different categories of risk factors. For continuous variables, (cholesterol, SBP, DBP, BMI) and a categorical variable, (smoking), incidence rates are given for subjects above and below the selected cut-off points i.e. 250 mg/dl for cholesterol, 160 mmHg for SBP, 95 mmHg for DBP, 27 k/m^2 for BMI. Incidence was significantly higher in high categories of SBP and BMI in both genders and DBP in males. After application of Bonferroni's inequality, SBP in both genders was no longer significant.

Table 13.6 shows the mean and standard error of the baseline characteristics in the index group compared with the comparison groups. Both males and females in the index group have higher SBP and they were slightly more overweight than the control group. There were no significant differences in the age, DBP or serum cholesterol and percentage of cigarette smoking (females) between the index and the comparison groups. After application of Bonferroni's inequality, the BMI in both genders was no longer significant. The positive relationship between the initial casual blood glucose and BMI, SBP

in both men and women and negative association of DBP in women was found to be significant by multiple regression analysis which included age, gender, serum cholesterol, BMI and blood pressure, as other variables. The negative association of DBP is due to interaction between SBP and DBP. After application of Bonferroni's inequalities, SBP in males was no longer significant.

For further analyses of the effect of SBP, DBP, serum cholesterol, BMI or cigarette smoking on the relationship between casual blood glucose level and progress to diabetes, variables were dichotomized in the index and comparison groups. In Table 13.7, incidence rates are shown for the index and comparison groups according to the possible effects of risk factors. As shown in Table 13.7, the 12-14 year incidence rate of progress to diabetes is remarkably increased above the 95th centile of casual blood glucose irrespective of the level of SBP, DBP, serum cholesterol, BMI or smoking in both genders, though the association was stronger in women. Incidence rates accounted for 10.5 (male 11.6, female 9.2) per 1,000 PYO in the index group, whereas only 0.93 (male 1.3, female 0.6) per 1,000 PYO were attributed in the comparison group. Progress to diabetes was found to be about 9 times more frequently in men and 15 times more frequently in women in the index group. For high BMI compared to low BMI in women, the relative risk of progress to diabetes is significantly greater in the index group, even after application of Bonferroni's inequality. The index-comparison relative risk for high BMI in both men and women and female cigarette smokers is greater, while for

the rest of the risk factors, in both genders, the index-comparison relative risk is greater in the lower risk groups.

Table 13.8 shows the sensitivity, specificity and positive and negative predictive value of casual post-prandial blood glucose value to 12-14 years worsening to diabetes in men and women with BMI greater and less than 27 Kg/m^2. The positive predictive value of worsening to diabetes was 7.2% (male 10.4% and women 4.2%) and the negative predictive value was 99% (male 98.5%, female 99.3%) when BMI was less than 27 Kg/m^2. When BMI was >27 Kg/m^2, the positive predictive value became 21.7% (male 19.1%, female 25%) and the negative predictive value 98.4% (male 97.9%, female 99%). Comparison of the relative risks of the index and comparison groups in this bivariate analysis provides evidence of only an association between casual blood glucose and BMI. To examine this further a MLR with an interaction term between blood glucose and rest of the variables was carried out.

Gender: The incidence of progression to diabetes in males and females in the various subgroups is given in Table 13.5. The incidence rates were higher in all categories in men rather than women and a higher age dependency was observed in females than in males. This gender difference was less marked in high categories of sugar, SBP and BMI rather than in the low categories. However, deterioration occurred more frequently in males than females for all subgroups, but the tendency towards worsening to diabetes within 12-14 years compared to the

control group, was more pronounced in females than males (Table 13.7).

The mean and standard error of the baseline variables for males and females in the index and comparison groups were also compared in Table 13.6. There were no gender differentials in mean values of baseline variables except serum cholesterol which in both groups was higher in females than males.

13.3.2.Multiple Logistic Regression Analysis

The univariate and bivariate analyses clearly indicate that the role of high casual post-prandial blood glucose as a risk factor for progress to diabetes can be properly evaluated only by taking account of confounding effects of other risk factors. Therefore, the relationship of baseline variables with deterioration to diabetes within 12-14 years was examined further with a MLR model to which the following 'predictors' were fitted: age, gender, BMI, SBP, DBP, serum cholesterol, cigarette smoking and blood glucose. All of the variables were dichotomized as before.

The baseline variables most powerfully predicting the development of diabetes were initial casual blood glucose values greater than 126 mg/dl and BMI above 27 Kg/m^2, none of the other variables approaching conventional statistical significance (Table 13.9). When analysis was repeated with continuous variables, sugar and DBP became significant. In the model with an interaction term, there was no significant association between sugar and rest of the variables as a predictor variable for worsening to diabetes. From the coefficient, from the logistic model,

for any difference in deterioration to diabetes by age, gender, degree of blood glucose, blood pressure, obesity or smoking, a ratio can be calculated expressing the relative odds of progress to diabetes in the 12-14 year period. The SOR of progress to diabetes has been calculated. This standardized estimated relative risk is approximately 12 times higher in the index than in the control group and about 3 times higher in high BMI categories than low BMI categories. Several of the risk factors are significantly correlated with each other and BMI and blood pressure are correlated with blood sugar (Table 13.6). To assess the independent relationship of each variables with progress to diabetes, another MLR analysis has been carried out for the index and comparison groups separately (Table 13.10). For the comparison group none of the variables was significantly related to progress to diabetes. However in the comparison group, the number of diabetes was relatively small and caution must be exercised in the interpretation of the results. In the index group the most powerful predictor of the development of diabetes was BMI. Again, none of the other variables approached conventional statistical significance.

13.4.DISCUSSION

The factors predicting metabolic deterioration are controversial. Impaired glucose tolerance is of interest with respect both to the possibility of its use as an early indicator of diabetes and to its relation to CVD (329, 330). This chapter concerns aspects related to diabetes. While the CVD mortality aspect is discussed in

Chapter 6. To determine the value of a high single casual blood glucose in predicting the subsequent development of overt diabetes, we preferred to use presence of classic diagnostic criteria of diabetes by means of record linkage with GP's records. In this study individuals identified by high casual blood glucose level were compared with those with low blood glucose level and observed for a long time, and GP's plus others diagnosis of treatments recorded in GP records was employed as the sole gauge of previous diabetes. The diagnostic criteria for diagnosis of diabetes by GP were based on unequivocal symptoms or signs of diabetes mellitus and/or standard glucose tolerance test (GTT) and were considered sufficiently reliable to remove any doubt of the presence of diabetes. All of the patients were under treatment for diabetes.

We believe that this indirect method of follow-up of a cohort has great advantages in a population survey study. 1) The entire population can be studied regardless of occupation, age, and infirmity or socio-economical characteristics. 2) A relationship which normally exist between doctor and patient encourages the co-operation of individuals, which is the largest factor in achieving a high response rate. 3) The population is easily studied. 4) Close involvement of the hospital consultants with the participating GP ensures a definite policy in the management of those individuals discovered to have a diabetic or incidental abnormality. 5) Advice and treatment can be administered firmly and consistently. There have been several follow-up studies (315-326) on unselected populations screened for blood sugar, though

only four have published data on factors predicting metabolic deterioration, and reviewed by Jarrett et al. (323). Each of these differs in the methods used and in the criteria adopted in defining the development of diabetes. None of them used casual blood glucose and GP's record linkage to predict deterioration to diabetes as we did in this analysis. O'Sullivan and Mahan in the Oxford Massachusetts Survey (315) used post-prandial venous blood sugar levels of 140 mg/dl or more, or capillary blood sugar levels of 170 mg/dl or more. The subjects were subsequently tested at varying intervals over 17 years, during which three markers of new diabetes were recognized (a) receiving insulin treatment, (b) people with blood sugar persistently exceeding 200 mg/dl post-prandial or 140 mg/dl fasting and (c) as for (b) except that post-prandial levels were 170 mg/dl and fasting levels 130 mg/dl. A control group with initial post-prandial blood sugar levels below 140 mg/dl was also studied. The median period of follow-up was about 14 years. Compared with the control group, diabetes occurred 5 times more frequently in people with initial post-prandial blood glucose from 140-169 mg/dl and 15 times more frequently in those with blood glucose of more than 169 mg/dl. Diabetes also occurred very much more frequently in people 20% above ideal body weight when their initial blood sugar level exceeded 169 mg/dl, with a smaller excess when blood sugar levels were in the range 140-169 mg/dl, a finding which this study also supports when casual post-prandial blood glucose (venous whole blood) was greater than 126 mg/dl.

Overweight people with initially "normal" blood glucose did not appear to be at greater risk. This finding was also supported by the present as well as the Whitehall (325) study. In the Birmingham Diabetes Survey (318) 50 g. oral glucose tolerance tests were used on 465 people with glucosuria and 343 people selected at random from the non-glycosuric population. Two follow-up reports have appeared, one at 5 years (317) and one at 10 years (318). "Florid diabetes" was defined as those with fasting blood glucose levels exceeding 130 mg/dl and "GTT diabetes" as those with fasting levels less than this, but with one-hour levels above 180 mg/dl and a 2 hour levels above 120 mg/dl. 45% of those with GTT diabetes progress to florid diabetes in ten years and, in general, the higher the blood glucose levels in the initial test, the more likely was a progression to florid diabetes. The authors did not relate body weight to subsequent diabetes. O'Sullivan and Mahan (319) studied 352 females identified as "chemical diabetes" by one of three criteria -(a) Mosenthal and Barry, (b) Fajans and Conn, (c) U.S. Public Health Service (USPHS). They were followed for 1-12 years. Clinical diabetes was diagnosed during follow-up if the fasting blood glucose exceeded 120 mg/dl or the post-prandial blood glucose exceeded 180 mg/dl or the post-prandial blood glucose within three hours of ingestion exceeded 300 mg/dl. The USPHS criteria were the best predictors of worsening to diabetes. The members of the group as a whole was overweight when diagnosed as in this study. In those overweight there was a significant excess of diabetes in all three diagnostic groups. Jarrett et al. in the

Whitehall Study (325) investigated 240 men identified as "borderline diabetics" by one of two criteria -(a) a survey blood sugar between 110-199 mg/dl and at standard GTT, (b) peak blood glucose 180 mg/dl or more and two hour blood sugar between 120-199 mg/dl and/or two value exceeding 180 mg/dl and/or mean two hours blood glucose 120 mg/dl or more. Overt diabetes was diagnosed during follow-up if there were (a) two successive two hours post-glucose blood sugar was greater than 200 mg/dl (b) three non-successive two-hour blood sugar was greater than 200 mg/dl (c) there was a development of unequivocal symptoms or signs of diabetes mellitus (d) a two-hours blood glucose was greater than 200 mg/dl at a standard afternoon oral glucose tolerance test. They reported that the levels of blood glucose themselves best predict worsening to diabetes. Obesity did not contribute to prediction. Authors reported that the fasting and two hours post glucose tolerance load have approximately the same effect upon the logistic function. In this study we used a single casual post-prandial blood glucose (whole blood) measured at baseline and defined as "asymptomatic hyperglycaemia" if blood sugar level 126 mg/dl or more (top 5% of distribution). Clinical diabetes was diagnosed during follow-up by the GP or incidentally during hospitalization for other causes and were under treatment for diabetes. Overall this study and published literature shows that in spite of different population groups, selected in different ways using different criteria in defining deterioration to diabetes, this study and four others (315, 316, 319, 325)

confirm that the levels of blood glucose are the best predictors of subsequent development of diabetes independent of how definition of diabetes or the particular glucose test used. The influence of obesity as a predictor is less clear. The Whitehall study (325) found no relationship between BMI and worsening to diabetes, while in this study and two American studies (315, 319) obesity appeared to contribute to prediction. In this study the index group as a whole was more overweight than controls, comparable with O'Sullivan and Mahan findings (315, 319, 326), and had higher blood pressure. There were associations between blood pressure, BMI and blood sugar levels independent of age, gender, and serum cholesterol at the initial examination as indicated by MLR analysis. Rates of deterioration to diabetes in this analysis showed a clear relation to the casual blood glucose level and were markedly influenced by the presence of obesity and hypertension in bivariate analysis. The effect of hypertension was removed, but the effect of obesity remained, when multivariate analysis was taken into account. In MLR analysis, when continuous rather than categorical variables were considered, DBP contributed to the prediction of worsening to diabetes independently, though when we analysed for the index group alone, there was no further evidence that DBP was a predictor of progression to diabetes. This suggests that the level of DBP may be more important than selected cut off points. The strong association between BMI and diabetes is confirmed, in that being grossly overweight and having a high blood glucose level at the time of initial examination increased the

probability of progress to clinical diabetes.

In this study, the higher casual post-prandial blood glucose level may be considered meaningful, in terms of future overt diabetes, as indications of potential rather than actual disease. The alternative end point, that higher mortality, in the extreme upper end of the casual blood glucose distribution (Chapter 6) confirmed the pernicious effect of high symptomless casual blood glucose. The trend of progression to higher blood sugar levels, and the number that go on to a deteriorated state, and higher mortality support this assessment.

CHAPTER 14

GENERAL DISCUSSION

14.1.INTRODUCTION

CVD is a major health problem in most parts of the world and leads to more deaths, disability and economic loss than any other disease. In industrialized countries improving the health of the population depends upon controlling CVD. A major goal of epidemiological research is to identify factors involved in the aetiology of diseases to prevent or control such diseases.

The aims of this study were to examine (1) the quality of data available from Renfrew and Paisley survey and feasibility of such programmes, (2) to explore its use in answering a number of epidemiological questions in relation to blood glucose level, blood pressure, body weight, gender, diabetes and mortality and (3) to evaluate the potential for further follow-up studies using CHI.

14.2.FEASIBILITY OF A SCREENING PROGRAMME SUCH AS MIDSPAN

The review of programme feasibility as a whole must be related, on the one hand, to initial expectations and, on the other, to the data collection. The aim was to introduce a broad-range multiple screening programme gradually developing to its maximum extent, and without doubt these expectations were met. The programme was made feasible to a great extent because of the active participation of the population, the health and the voluntary organizations and the mass media.

14.3.QUALITY OF INITIAL DATA

All steps possible, including the use of

internationally standardised questionnaires and method of laboratory tests as well as anthropometric and clinical and physiological measurements, were taken with the aim of collecting good quality data. Analysis carried out in this project, for example comparisons with the General Household Survey and other surveys, by checking ranges and distributions of values etc. suggests that the aim of collecting good quality data was, on the whole, achieved. The one exception to this was the large number of missing values for blood glucose, but as this was largely due to administrative and financial problems it is unlikely to have caused any major bias.

In blood pressure measurement, errors in measurement due to large arm size were unpredictable and non-linear. The standard commercial cuff of 12X22 cm used in the Renfrew and Paisley studies should have been replaced with the recommended size of 30 Cm in length (334). However it seems reasonable to regard the blood pressure measurements, in general, as being of good quality.

Relatively large samples were used to allow for the detection of changes that may not have been significant for an individual but were significant for the whole population. This also allowed a breakdown into subgroups.

We can therefore conclude that the initial data set provides a valid basis for mortality and morbidity follow-up studies.

14.4.MORTALITY SURVEILLANCE

Monitoring cardiovascular morbidity and mortality at the community level has many problems. The problems in monitoring strokes are the same as monitoring heart

disease. All cardiovascular registers (including stroke and heart disease) and diagnostic criteria (defined by ICD) are purely clinical. However, it has been concluded that although the sub-diagnosis (type of stroke or heart disease) was unreliable, the stroke and heart disease diagnoses as a whole were consistent and reliable (332). Mortality data for evaluating CVD have known limitations for defining cause-specific mortality. This is true especially in areas such as the west of Scotland where autopsy rates are relatively low (333). The observed rates depend on physicians habits in completing death certificates. Age and gender-specific total mortality rates would be the most reliable indices under these conditions as used throughout this study. However, they lack sensitivity because mortality is the end point in the course of CVD, and only part of the total mortality is due to CVD.

The standardized mortality ratio in Renfrew and Paisley was lower than one, and the number of expected deaths exceed the observed deaths. This difference was probably largely due to under reporting of mortality data by NHSCR. On the other hand, the response rate for the initial Renfrew and Paisley survey was about 80% and there is the likelihood that some people did not participate in the study because of illness. This may explain the lower standard mortality ratio in the first years of the study. As the under-reporting is due to 'administrative' errors it is likely that the under-reporting affects all patients groups equally. Therefore it is unlikely to affect the study of risk factors for mortality, however this may well

deserve further attention. Cross-sectional studies have important limitations in study of CVD. Thus, underlying severe atherosclerosis may exist with no clinical manifestation. In fact, cross-sectional analysis does not give an accurate picture of a sequence of events. i.e. it cannot determine if the hyperglycaemia preceeded arteriosclerosis or vice versa. Therefore, in spite of limitations of the mortality data as described above, this study provides a better test of the association between baseline variables and CVD mortality outcome than is possible with cross-sectional studies.

14.5.RISK FACTORS PREDICTIVE OF MORTALITY

For the first time, the Renfrew and Paisley study has allowed association between various CVD risk factors and mortality to be examined. It has produced new findings. Variation in mortality risk has been examined while adjusting for seven CVD risk factors (age, gender, SBP, DBP, serum cholesterol, blood glucose, BMI, and smoking) in a series of age-adjusted and MLR analyses.

The main aim has been to re-test the hypothesis that high casual blood glucose is a risk factor for all causes, CVD, IHD and stroke mortality. A positive association between initial casual blood glucose level and subsequent mortality was found. Most previously published studies of asymptomatic hyperglycaemia had only included males so it was decided that gender differences should be analysed in more detail. High blood glucose level was a risk factor for CVD mortality in both genders. It was also a risk factor for all causes, IHD and stroke mortality in women but in men was of borderline significance. On the other

hand, repeating the original MLR analysis and controlling the influence of gender, along with seven other cardiovascular risk factors simultaneously showed that those cardiovascular risk factors do not account for the overall gender difference in mortality rates. Some other studies had suggested that blood glucose levels are associated with other CVD risk factors, particularly with BMI, so it was decided to investigate the extent to which blood glucose level interacts with BMI in the prediction of all causes and CVD mortality. There was no relationship between BMI and CVD deaths neither for normoglycaemics nor hyperglycaemics. Lastly, as there was conflicting evidence in the literature, the relative importance of SBP compared to DBP and other combinations of SBP and DBP in predicting the risk of IHD and stroke mortality were re-examined. The risk of IHD deaths was more strongly associated with MAI and single SBP in both males and females. SBP and DBP together, MAP and PP do not predict future IHD mortality better than SBP alone or MAI. SBP and DBP are strongly correlated in both genders but their relationship with stroke mortality was different among males and females. In females the risk of stroke mortality was more strongly associated with DBP; in males SBP and DBP have the same predictive strength of stroke death.

In this study asymptomatic hyperglycaemia was defined as a casual post-prandial blood glucose level above the 95th percentile cut-point (126 mg/dl). However a word of caution is needed. The problem is whether casual blood glucose is a sufficiently sensitive measure. These

arbitrary criteria are at variance with those for diabetes and impaired glucose tolerance based on fasting blood sugar levels or the standard glucose tolerance test that have been proposed by the National Diabetes Data Group (171) and recommended by the World Health Organization (172). However, in an epidemiological investigation, examining a large cohort of the community, it is rather difficult to require that all subjects arrive in the fasting state or to require that they remain for 2 hours after glucose challenge, plus it is seldom practical to determine several glucose values from an economical point of view. On the other hand, casual and various post-challenge glucose determinations yield remarkably similar results in different studies (41, 43, 143, 167).

14.6.RISK FACTORS FOR DEVELOPMENT OF DIABETES

This study showed that an initial casual blood glucose level was related to non-insulin-dependent diabetes mellitus in a maximum of 14 years follow-up. Of the base-line variables BMI was also significantly predictive of ultimate worsening to diabetes.

The use of a casual blood glucose in Midspan provided a new and unique opportunity to examine the usefulness of this measurement. Its use for screening in general practice seems a cheap and easy method of identifying patients at risk.

14.7.FOLLOW-UP OF SURVIVORS

Two methods of record linkage could be used to follow-up this cohort based on record linkage with SHIPS (SMR-1) files in the ISD and/or by using the CHI and general practitioner records.

SMR-1 data, can be used to produce details of diagnosis and outcome on hospital admission. There are advantages in being able to conduct long-term follow-ups indirectly in this way with relatively little expense and no physical re-examination especially when economy is a prime consideration. However, there are a number of reasons why it may be preferable to use the second method of linkage using the CHI and GP records.

1. SMR-1 data obviously only refer to in-patient admissions and often little is known about hospitalization rates. For example, the proportion of diabetics who are hospitalized and recorded as diabetics is small so that the number of asymptomatic hyperglycaemics who later had diabetes diagnosed could not be estimated.

2. Linkage with SMR-1 data has been tried before (310) giving a sensitivity of 81% for in-patient data for one year (1973). This is likely to decrease for subsequent years because of changes in clinical practice and admission policies producing fairly low sensitivity.

This study has shown that record linkage with the CHI is feasible and that further studies would be worthwile.

14.8. CONCLUSIONS

Based on the results of 10-14 years follow-up of this population-based cohort study in Renfrew and Paisley, the following conclusions have been made:

1. The programme was feasible. The participation rate was in order of about 80%, and the reactions of the people, health personnel and the local administrators and managers was generally positive.

2.There was an association between high casual blood glucose defined as the upper 5% of casual blood glucose value and subsequent mortality from all causes, CVD, IHD and stroke.

3.This association was dependent on gender for all causes, IHD and stroke mortality. However, females with high casual blood glucose value were more susceptible to mortality outcome than men.

4.There was no significant interaction between BMI and casual blood glucose level.

5.Considered CVD risk factors do not account for the overall gender differential in mortality.

6.The risk of IHD death was more strongly associated with SBP than DBP in both genders.

7.The risk of stroke death was more strongly associated with DBP than SBP in women, while in men the DBP was as good a predictor of stroke mortality as SBP.

8.Follow-up studies looking at morbidity in GP records are possible using the CHI and further studies should be carried out to identify the test practical approach.

9.Initial high casual post-prandial blood glucose level was related to non-insulin-dependent diabetes mellitus during the follow-up period. Deterioration, however, was also closely related to body weight.

14.9.FURTHER STUDIES

The Midspan database will only achieve its full potential if it is maintained efficiently and effectively, a full range of end point information (including morbidity) is linked to it, and appropriate access can be achieved easily. Preliminary record linkage studies with

CHI have been very successful with about 95% of patients contacted through mail or their GP, but a more systematic approach to the use of the CHI needs to be explored.

This study has identified a number of problems. These include identification of the underreporting of deaths through record linkage with NHSCR, difficulties in locating and maintaining archived data tapes and other information stores, and continuing problems in the safe storage of the original data collection forms.

Further operational studies, on the development and assessment of a robust system for the management of Midspan, the methodology of which can be applied to any similar well-population register are required. These further studies include:

a) the identification and detailed description of the activities necessary to maintain and manage the register within the context of the Scottish Health Service.

b) the identification and analysis of problems in the maintenance and use of the register and their possible solutions.

c) the further investigation and improvement of record linkage with NHSCR and CHI.

d) the development of methods, including manual and microcomputer based systems, which will facilitate the use of the register and potentially make it available to a wider group of research workers.

e) the development of the educational potential of such a register for use in the continuing education of epidemiological and health service research workers.

USE AND EVALUATION OF A REGISTER FOR A WELL POPULATION IN STUDIES ON CARDIOVASCULAR DISEASE AND DIABETES IN THE WEST OF SCOTLAND

BY

© MOHSEN JANGHORBANI M.Sc.

THESIS SUBMITTED IN PARTIAL SATISFACTION OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

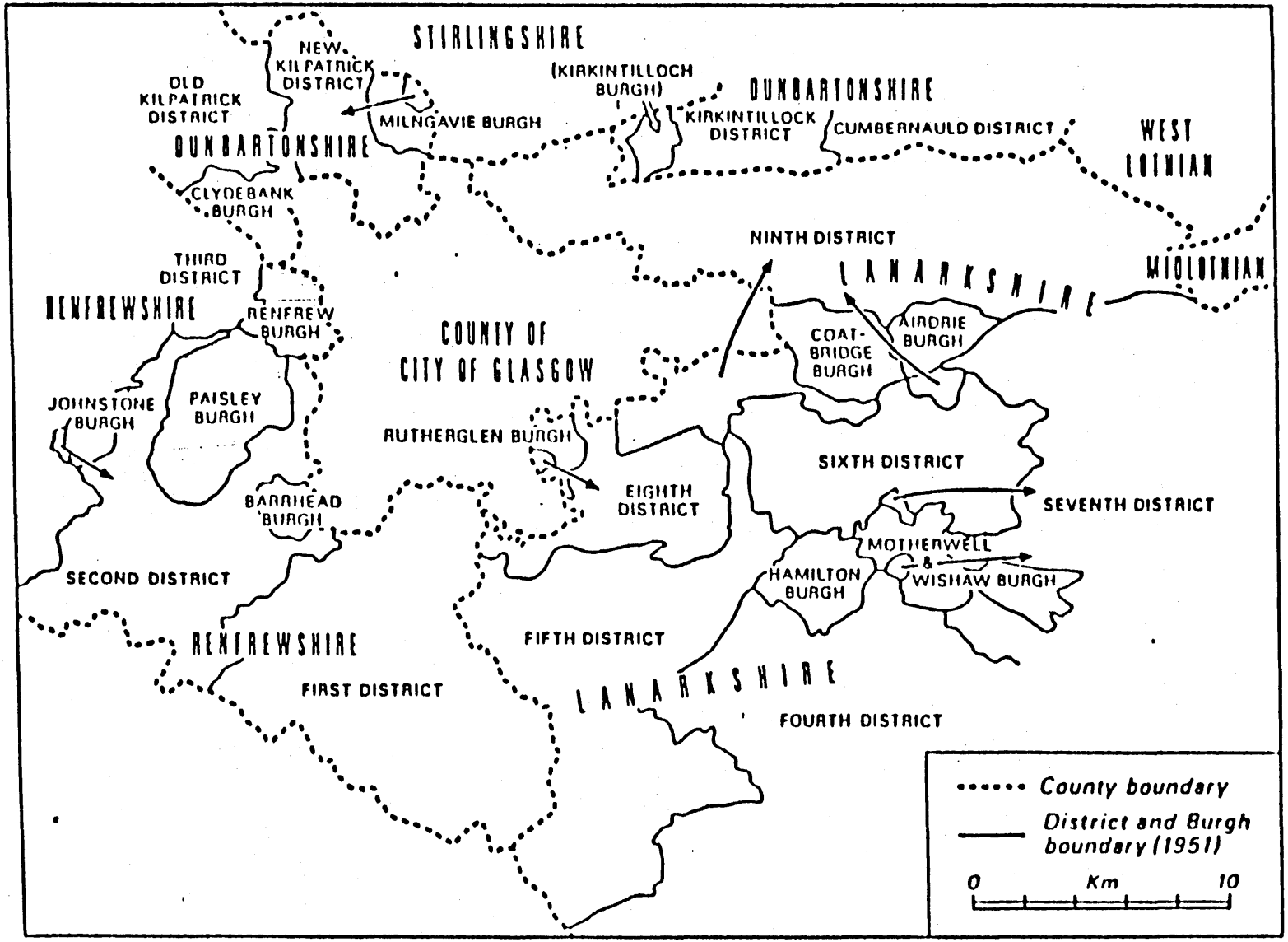
TO

THE DEPARTMENT OF COMMUNITY MEDICINE

FACULTY OF MEDICINE

UNIVERSITY OF GLASGOW

VOLUME 2



MAP 1.1.Glasgow Boundary Extension.

TABLE 1.1. Renfrew and Paisley Midspan Health Survey Household Census and Examination Response Rates.

Paisley Sectors	Households	Reply Rate (%)	Individual Eligible	Individual Examined	Response Rate (%)
Glenburn	3,518	96.8	2,334	1,851	79.3
Foxbar	3,505	97.4	1,821	1,435	78.8
Mossvale	2,492	96.5	959	660	68.8
Hunterhill	1,658	97.7	870	672	77.2
Whitehaugh	4,527	96.6	2.029	1,512	74.5
Gallowhill	2,923	96.9	1,756	1,323	75.3
Lochfield	4,008	98.3	2,214	1,678	79.4
Ferguslie	3,150	92.9	993	580	58.4
Bredilands	2,292	96.5	1,088	845	77.7
Central	4,356	97.6	1,949	1,370	70.3
10 Sector Combined	32,429	96.8	16,013	11,926	74.5
All non-respondents reinvited			4,087	520	12.8
Survey Combined	32,429	96.8	15,971	12,446	77.9
Renfrew	6,534	99.1	3,810	3,000	78.8
Combined Renfrew and Paisley	38,963	97.2	19,781	15446	78.1

Source: (15).

TABLE 4.1.Baseline Survey by Area, Age and Gender.

Age Group (Year)	Renfrew		Paisley		Both Renfrew and Paisley Combined	
	Male(%)	Female(%)	Male(%)	Female(%)	Male(%)	Female(%)
45-49	391(28.6)	426(27.5)	1427(25.5)	1608(24.0)	1818(26.1)	2034(24.7)
50-54	366(26.8)	418(27.0)	1597(28.5)	1856(27.7)	1963(28.2)	2274(27.6)
55-59	336(24.6)	366(23.6)	1322(23.6)	1637(24.5)	1658(23.8)	2003(24.3)
60-64	273(20.0)	338(21.8)	1257(22.4)	1590(23.8)	1530(22.0)	1928(23.4)
All Ages	1366(100)	1548(100)	5603(100)	6691(100)	6969(100)	8239(100)

TABLE 4.2. Study Population, Age, Gender Distribution, Numbers Excluded, Numbers in Mortality Studies.

Age Group	Total Number			Excluded Known Diabetes			No. at Risk for Mortality study After Exclusion		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
45-49	1174	1365	2539	6	9	15	1168	1356	2524
50-54	1295	1546	2841	17	10	27	1278	1536	2814
55-59	1175	1457	2632	22	21	43	1153	1436	2588
60-64	1116	1413	2529	17	24	41	1099	1389	2488
45-64	4760	5781	10541	62	64	126	4698	5717	10415

Unknown diabetic status=5 and Excluded.

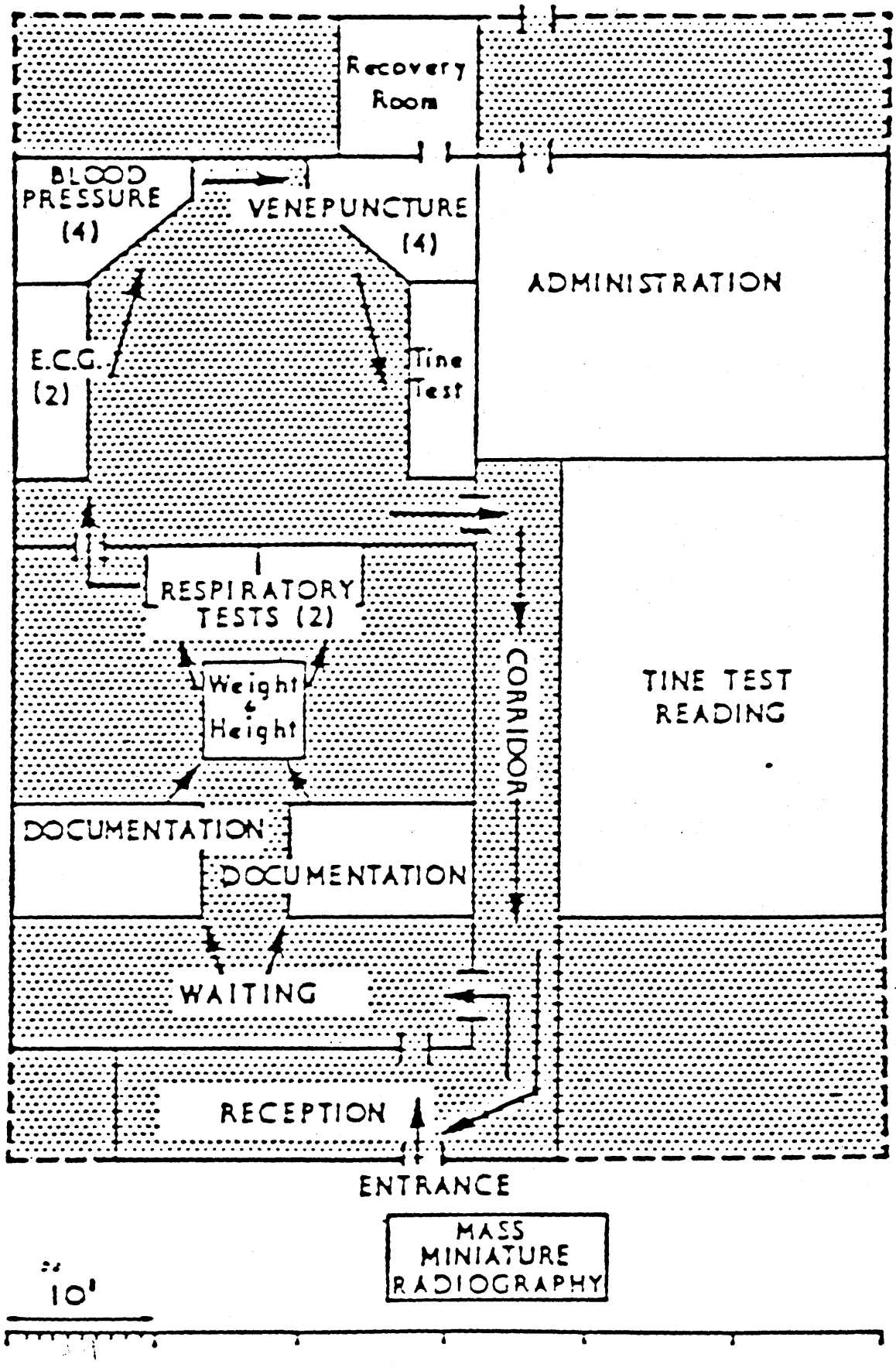


FIGURE 4.1. Plan of Temporary Examination Centre in Renfrew Town Hall. Numbers of Staff Operating Each Unit Are Given in Brackets.

TABLE 5.1. Percentage of Cigarette Smoking Habits of Men and Women.

Smoking Categories	Male					Female				
	Age at Entry					Age at Entry				
	45-49	50-54	55-59	60-64	All Ages	45-49	50-54	55-59	60-64	All Ages
Never-smokers	20.6	19.3	20.5	20.7	20.2	41.8	44.2	50.8	56.6	42.3
Current Smok.	55.6	50.7	50.1	48.1	51.3	50.8	45.6	40.3	30.9	42.2
Ex-smokers	23.8	30.0	29.4	31.2	28.5	7.4	10.2	8.9	12.5	15.5
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

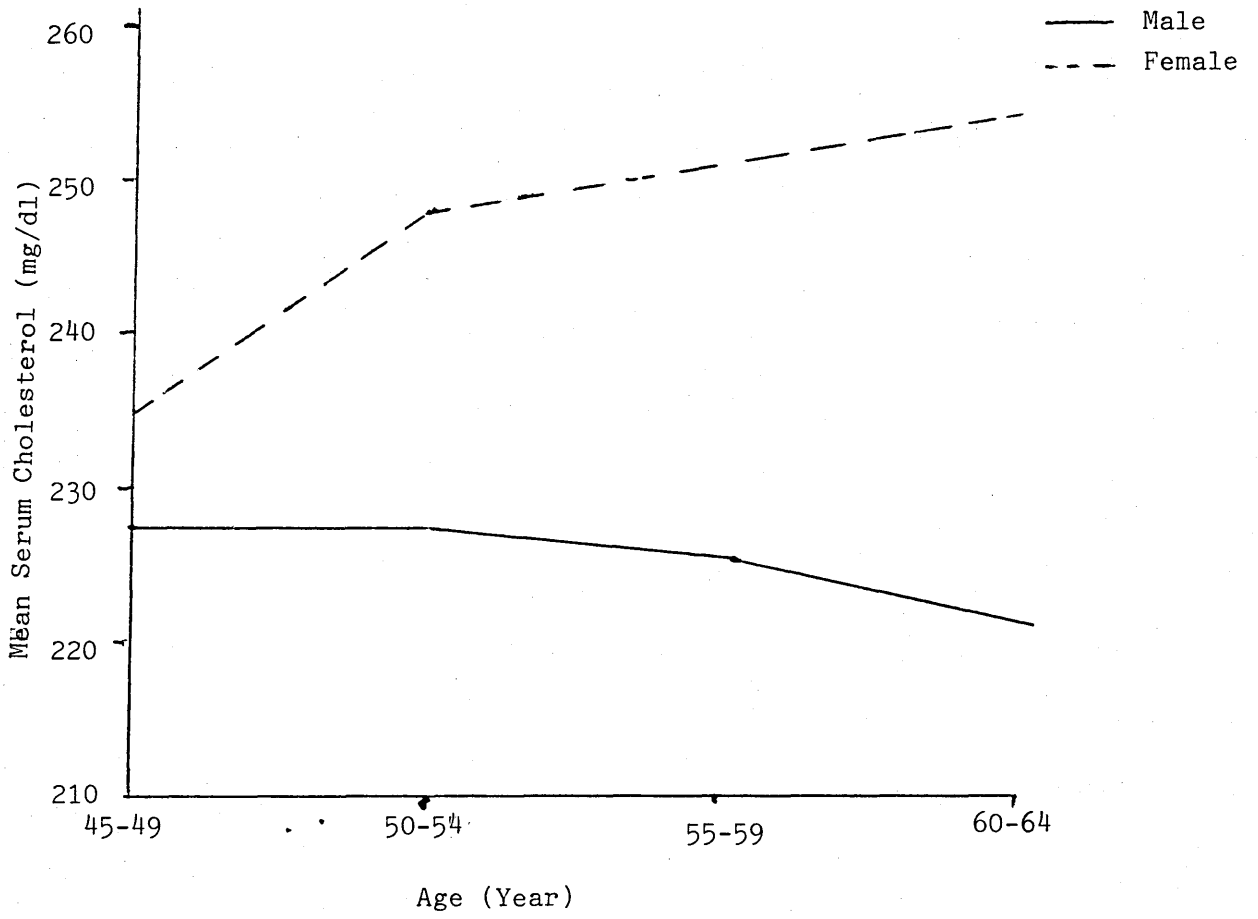


FIGURE 5.1.Mean Serum Cholesterol Value by Age and Gender.

TABLE 5.2. Percent Distribution of Serum Cholesterol of men and Women.

Serum Cholesterol (mg/dl)	Male					Female				
	Age at Entry					Age at Entry				
	45-49	50-54	55-59	60-64	All Ages	45-49	50-54	55-59	60-64	All Ages
<199	23.8	22.2	24.8	27.4	24.4	19.6	11.0	10.5	8.1	12.3
200-219	18.5	20.3	20.2	21.2	20.0	16.7	11.8	10.5	10.1	12.3
220-239	22.7	22.6	22.4	24.1	22.9	21.9	21.7	19.0	19.2	20.5
240-259	16.5	16.1	15.2	14.2	15.6	17.0	19.0	20.8	20.0	19.2
260-279	10.2	10.5	9.0	6.8	9.3	12.1	16.0	15.6	17.0	15.2
280-299	5.2	4.8	5.0	3.6	4.7	6.5	10.0	11.8	10.8	9.8
300-319	1.9	2.1	1.9	1.6	1.9	2.8	5.6	6.3	7.4	5.5
320+	1.3	1.3	1.5	1.1	1.3	3.5	4.8	5.5	7.3	5.2
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

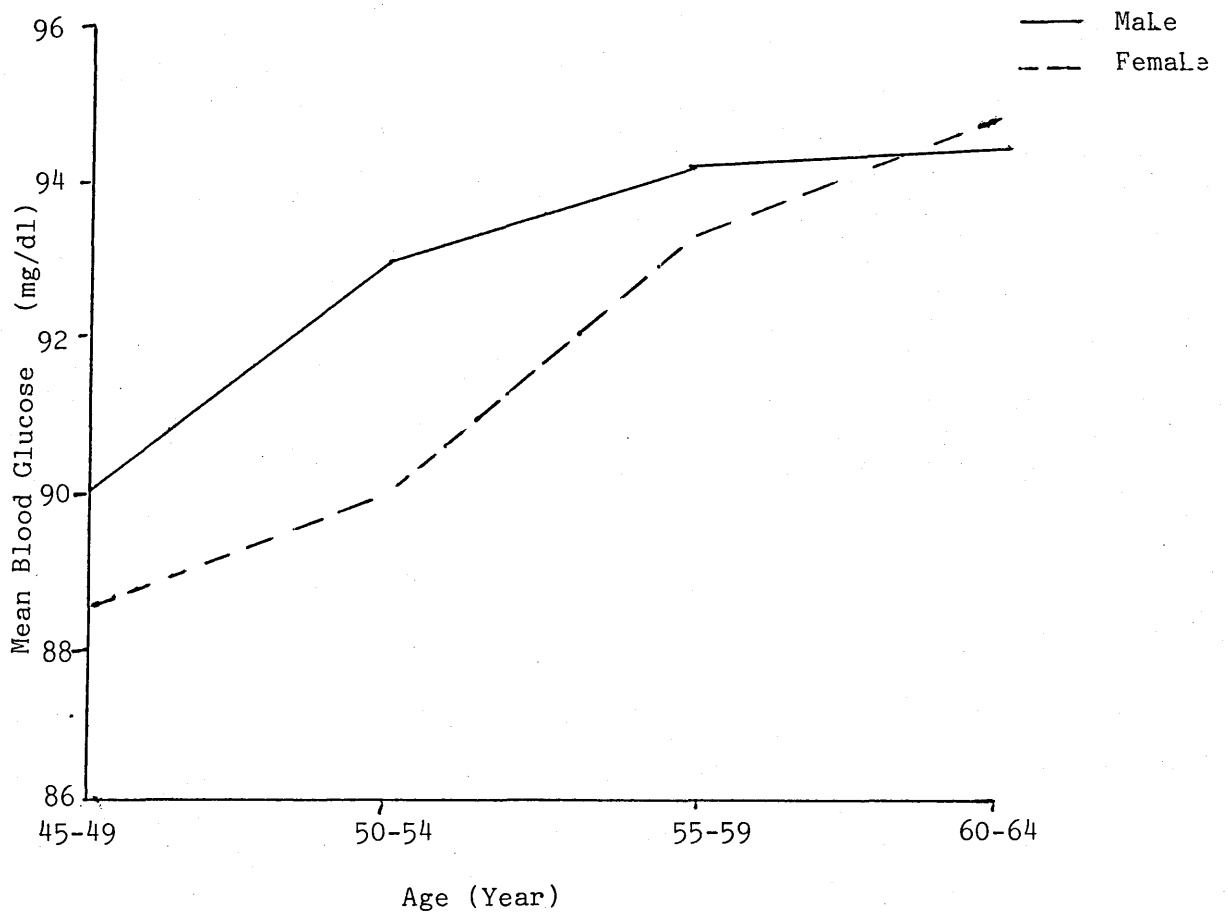


FIGURE 5.2. Mean Blood Glucose Values by Age and Gender.

TABLE 5.3. Percent Distribution of Casual blood glucose of Men and Women.

Blood Glucose (mg/dl)	Male					Female				
	Age at Entry					Age at Entry				
	45-49	50-54	55-59	60-64	All Ages	45-49	50-54	55-59	60-64	All Ages
<84	45.8	43.0	40.0	39.4	42.1	48.7	46.1	42.1	39.2	44.0
85-104	37.7	36.0	39.7	39.1	38.1	39.4	39.8	39.4	40.0	39.6
105-124	10.9	14.1	13.7	13.1	13.0	8.5	10.8	12.4	14.6	11.6
125-144	3.6	4.1	3.5	5.2	4.1	2.3	1.8	3.5	3.1	2.7
145-164	1.1	1.3	1.4	1.2	1.3	0.4	0.7	0.8	1.5	0.9
165-184	0.3	0.6	0.4	0.5	0.5	0.2	0.2	0.5	0.6	0.4
185-204	0.3	0.3	0.3	0.5	0.3	0.1	0.2	0.3	0.2	0.2
205+	0.3	0.6	1.0	0.8	0.7	0.3	0.4	1.0	0.9	0.6
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

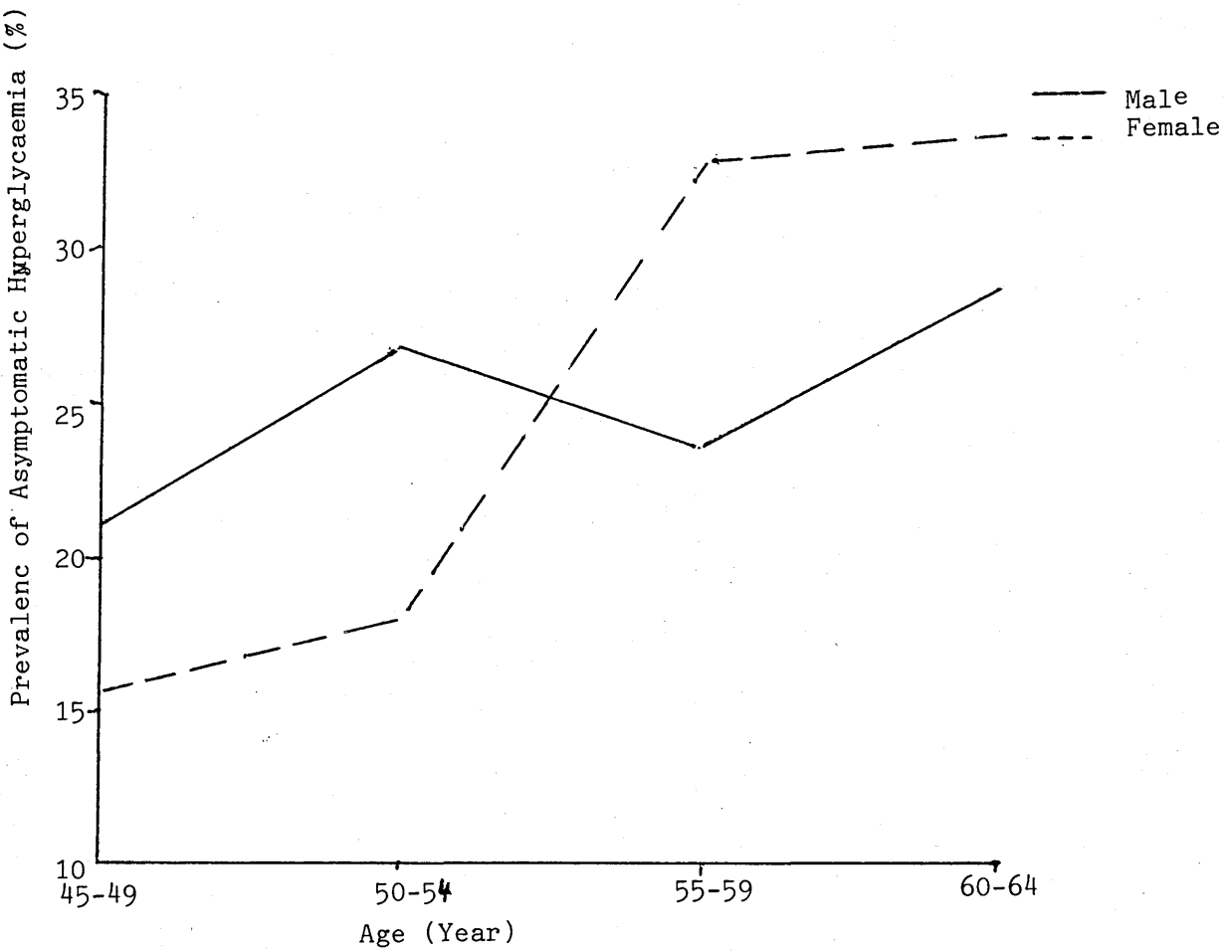


FIGURE 5.3. Prevalence of Asymptomatic Hyperglycaemia by Age and Gender.

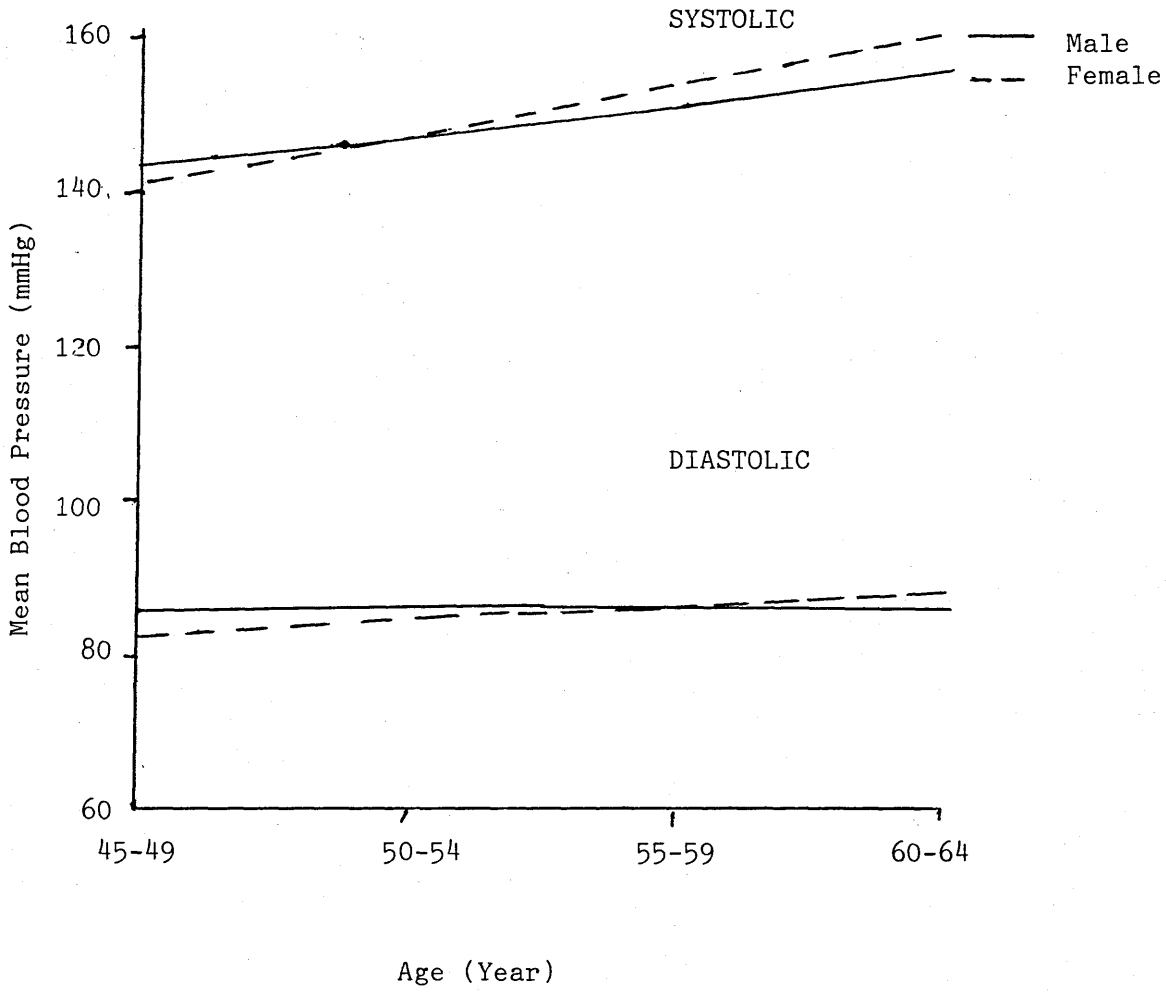


FIGURE 5.4.Mean Systolic and Diastolic blood Pressure Values by Age and Gender.

TABLE 5.4. Percent Distribution of Systolic Blood Pressure of Men and Women.

Systolic Pressure (mmHg)	Male					Female				
	Age at Entry					Age at Entry				
	45-49	50-54	55-59	60-64	All Ages	45-49	50-54	55-59	60-64	All Ages
<119	11.7	10.3	7.7	5.1	8.9	16.0	12.3	8.5	4.4	10.5
120-139	37.4	33.2	28.8	24.2	31.3	38.1	31.3	23.9	20.2	28.6
140-159	33.3	33.0	34.0	34.1	33.5	28.9	31.4	32.1	30.9	30.9
160-179	12.4	16.1	19.8	21.6	17.2	11.9	16.5	20.4	24.5	18.2
180-199	4.2	4.9	6.8	9.4	6.2	3.5	5.8	9.8	13.1	7.9
200+	1.0	2.4	3.0	5.6	2.9	1.6	2.7	5.3	6.9	4.0
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

TABLE 5.5. Percent Distribution of Diastolic Blood Pressure of Men and Women.

Diastolic Pressure (mmHg)	Male					Female				
	Age at Entry					Age at Entry				
	45-49	50-54	55-59	60-64	All Ages	45-49	50-54	55-59	60-64	All Ages
<64	3.0	3.2	4.1	5.4	3.9	6.4	5.4	4.8	4.8	5.4
65-74	18.7	16.8	17.9	18.0	17.8	24.1	18.9	17.8	15.4	19.1
75-84	30.9	32.1	29.3	29.2	30.5	32.7	32.8	29.6	25.9	30.4
85-94	27.2	27.9	25.6	23.7	26.3	23.0	24.9	24.9	27.1	25.0
95-104	13.1	12.6	15.1	14.7	13.8	9.4	11.1	14.9	15.5	12.7
105-114	5.1	4.8	5.3	6.0	5.2	2.7	4.8	6.2	7.6	5.3
115+	2.0	2.6	2.7	2.9	2.6	1.6	2.0	1.8	3.7	2.2
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

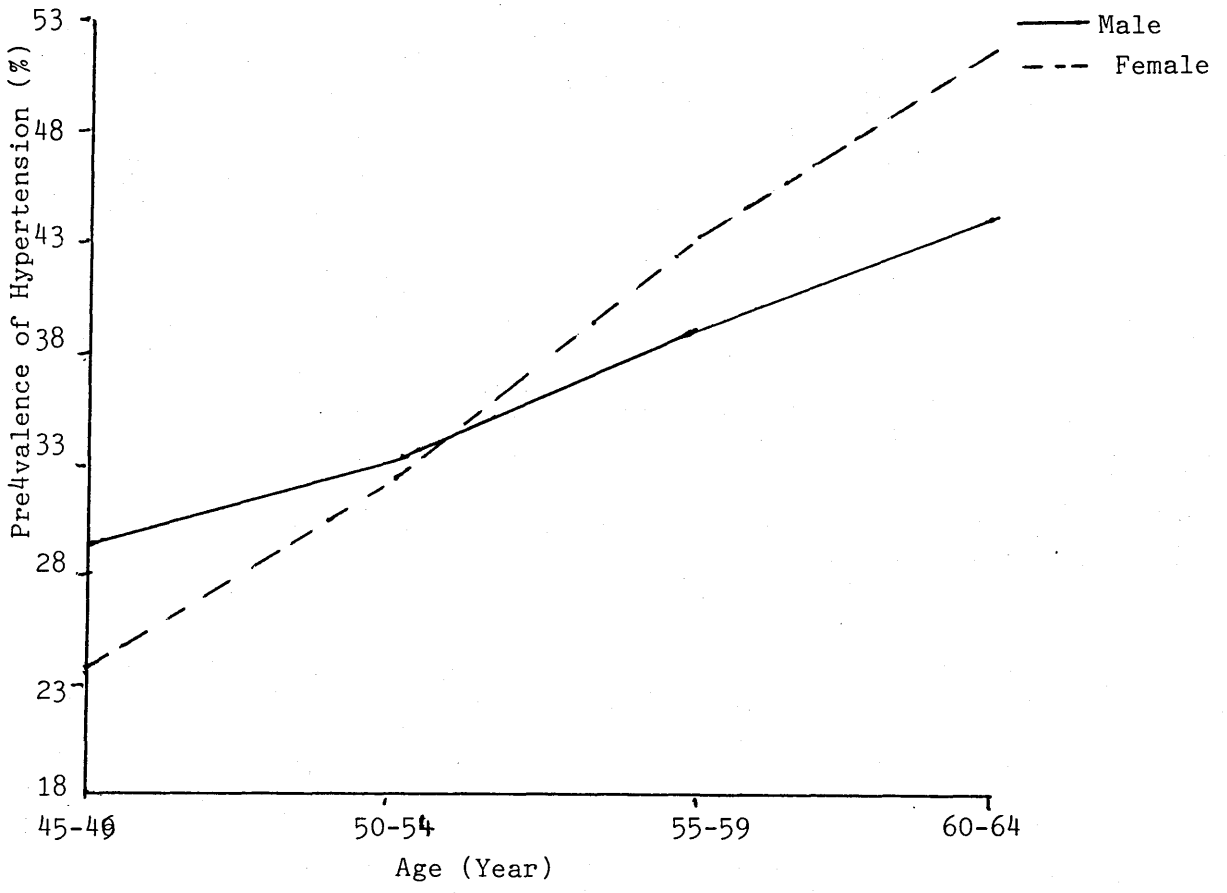


FIGURE 5.5. Prevalence of Hypertension by Age and Gender.

TABLE 5.6. Coefficient of Correlation Between Age, Systolic (SBP), Diastolic (DBP) Blood Pressure, Blood Sugar, Serum Cholesterol, Cigarette Smoking, and BMI in Men and Women.

Variable	SBP	DBP	Serum Choles.	Blood Glucose	BMI
Male					
Age	0.20***	0.00	-0.06***	0.05***	0.00
SBP		0.66***	0.03*	0.12***	0.20***
DBP			0.07***	0.02*	0.30***
Serum Choles.				-0.01	0.07***
Blood Glucose					0.16***
Female					
Age	0.28***	0.15***	0.16***	0.09***	0.10***
SBP		0.67***	0.08***	0.12***	0.29***
DBP			0.07***	0.04**	0.35***
Serum Choles.				0.00	0.06***
Blood Glucose					0.07***

*P<0.05, **P<0.01, ***P<0.001

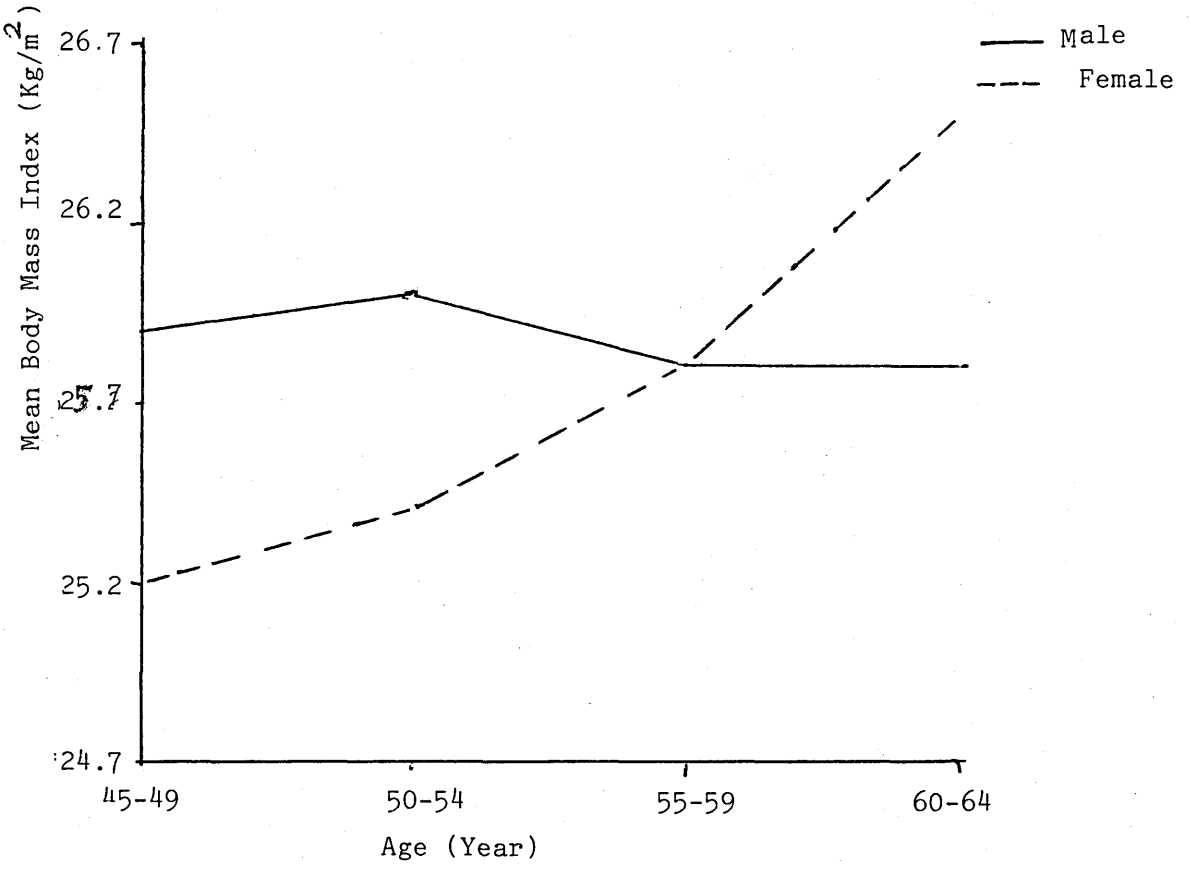


FIGURE 5.6. Mean Body Mass Index Values by Age and Gender.

TABLE 5.7. Percent Distribution of Body Mass Index of Men and Women.

BMI (Kg/m)	Male					Female				
	Age at Entry					Age at Entry				
	45-49	50-54	55-59	60-64	All Ages	45-49	50-54	55-59	60-64	All Ages
<23	19.0	19.4	19.8	21.2	19.8	30.6	28.5	28.4	22.9	27.7
23-27	46.9	44.5	44.9	43.5	45.0	41.4	41.4	36.4	36.8	39.1
27+	34.1	36.1	35.3	35.3	35.2	28.0	30.1	35.2	40.3	33.2
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

TABLE 5.8. Univariate Logistic Function Analysis of the 10-14 Years Risk of All Causes, CVD, IHD and Stroke Death Among Men.

Variable	Logistic Coefficient		Standardized Odds Ratio@		Z-Test	
	Crude	Age-Adjusted	Crude	Age-Adjusted	Crude	Age-Adjusted
All Causes 968 Deaths in 4789 men						
Age	0.1068	-	1.82	-	15.35***	-
Systolic BP	0.0146	0.0105	1.39	1.26	9.41***	6.52***
Diastolic BP	0.0148	0.0155	1.21	1.22	5.50***	5.59***
BMI	-0.0160	-0.0158	0.95	0.95	-1.50	-1.44
Serum Chol.	-0.0032	-0.0021	0.89	0.92	-3.28**	-2.16*
Blood Glucose	0.0033	0.0025	1.09	1.06	2.63**	1.97*
Cig. Smoking	0.5356	0.6365	2.92	3.57	7.32***	8.41***
Cardiovascular Disease 505 Deaths in 4326 Men						
Age	0.1118	-	1.85	-	12.21***	-
Systolic BP	0.0222	0.0183	1.63	1.49	11.21***	8.95***
Diastolic BP	0.0300	0.0304	1.47	1.47	8.69***	8.62***
BMI	0.0425	0.0440	1.15	1.16	3.08**	3.11**
Serum Chol.	0.0021	0.0034	1.08	1.13	1.65	2.61**
Blood Glucose	0.0044	0.0039	1.12	1.13	2.93**	2.46*
Cig. Smoking	0.3485	0.4491	2.01	2.45	3.66***	4.60***
Ischaemic Heart Disease 350 Deaths in 4171 Men						
Age	0.0963	-	1.70	-	9.15***	-
Systolic BP	0.0206	0.0171	1.57	1.45	8.89***	7.22***
Diastolic BP	0.0274	0.0279	1.42	1.43	6.69***	6.73***
BMI	0.0427	0.0437	1.15	1.15	2.63**	2.64**
Serum Chol.	0.0033	0.0044	1.13	1.18	2.20*	2.94**
Blood Glucose	0.0042	0.0037	1.11	1.10	2.32*	1.95
Cig. Smoking	0.2752	0.3580	1.73	2.05	2.46*	3.15**
Stroke 79 Death in 3900 Men						
Age	0.1463	-	2.23	-	6.38***	-
Systolic BP	0.0296	0.0253	1.91	1.74	6.94***	5.72***
Diastolic BP	0.0420	0.0413	1.71	1.70	5.67***	5.57***
BMI	0.0331	0.0336	1.11	1.12	0.99	0.98
Serum Chol.	-0.0006	-0.0011	0.98	1.04	-0.20	-0.35
Blood Glucose	0.0560	0.0050	1.15	1.13	1.96*	1.65
Cig. Smoking	0.3667	0.4940	2.08	2.68	1.60	2.14*

@Odds ratio computed as the antilogarithm of the original coefficients for a change in the risk factor by an amount equal to its standard deviation.

TABLE 5.9. Univariate Logistic Function Analysis of the 10-14 Years Risk of All Causes, CVD, IHD and Stroke Death Among Women.

Variable	Logistic Coefficient		Standardized Odds Ratio@		Z-Test	
	Crude	Age-Adjusted	Crude	Age-Adjusted	Crude	Age-Adjusted
All Causes 664 Deaths in 5817 Women						
Age	0.1073	-	1.80	-	13.31***	-
Systolic BP	0.0130	0.0077	1.37	1.21	8.32***	4.66***
Diastolic BP	0.0146	0.0086	1.21	1.12	4.85***	2.79**
BMI	-0.0023	-0.0167	0.99	0.93	-0.24	-1.74
Serum Chol.	-0.0002	-0.0022	1.01	0.91	-0.19	-2.13*
Blood Glucose	0.0093	0.0078	1.24	1.19	7.27***	6.13***
Cig. Smoking	0.3329	0.5282	1.95	2.87	4.02***	6.16***
Cardiovascular Disease 289 Deaths in 5442 Women						
Age	0.1479	-	2.25	-	11.64***	-
Systolic BP	0.0209	0.0146	1.66	1.43	9.48***	6.26***
Diastolic BP	0.0324	0.025	1.53	1.39	7.65***	5.73***
BMI	-0.0171	-0.0021	1.08	0.99	-1.28	-0.15
Serum Chol.	0.0050	0.0023	1.23	1.10	3.62***	1.57
Blood Glucose	0.0106	0.0091	1.27	1.23	7.04***	6.01***
Cig. Smoking	0.3767	0.6412	2.12	3.60	3.11**	5.12***
Ischaemic Heart Disease 168 Deaths in 5321 Women						
Age	0.1322	-	2.07	-	8.28***	-
Systolic BP	0.0208	0.0153	1.66	1.45	7.39***	5.15***
Diastolic BP	0.0281	0.0215	1.44	1.32	5.10***	3.82***
BMI	0.0352	0.0192	1.16	1.09	2.14*	1.14
Serum Chol.	0.0074	0.0051	1.36	1.23	4.22***	2.78**
Blood Glucose	0.0120	0.0110	1.31	1.28	7.00***	6.38***
Cig. Smoking	0.2682	0.5009	1.71	2.72	1.70	3.11**
Stroke 80 Death in 5232 Women						
Age	0.1510	-	2.29	-	6.36***	-
Systolic BP	0.0190	0.0124	1.59	1.35	4.66***	2.87**
Diastolic BP	0.0388	0.0317	1.66	1.51	5.13***	4.07***
BMI	-0.0363	-0.0556	0.85	0.79	-1.30	-1.98*
Serum Chol.	-0.0016	-0.0048	0.93	0.82	-0.58	-1.71
Blood Glucose	0.0105	0.0091	1.27	1.23	4.32***	3.61***
Cig. Smoking	0.7649	1.02	4.62	7.68	3.34***	4.38***

@Odds ratio computed as the antilogarithm of the original coefficients for a change in the risk factor by an amount equal to its standard deviation.

TABLE 5.10. Multiple Logistic Function Analysis of the 10-14 Years Risk of All Causes, CVD, IHD and Stroke Death Among Men and Women.

Variable	Male			Female		
	Logistic Coefficient	SOR@	Z-Test	Logistic Coefficient	SOR@	Z-Test
All Causes 968 Death in 4789 Men and 664 Deaths in 5817 Women						
Age	0.1075	1.82	14.69***	0.1036	1.79	12.13***
Systolic BP	0.0065	1.17	2.94**	0.0089	1.22	5.12***
Diastolic BP	0.0120	1.17	3.15**	0.0042	1.06	1.00
BMI	-0.0173	0.93	-1.46	-0.0215	0.93	-2.12*
Serum Chol.	-0.0018	0.93	-1.83	-0.0020	0.93	-1.93
Blood Glucose	0.0027	1.07	2.05*	0.0081	1.24	6.22***
Cig. Smoking£	0.3580	2.05	9.21***	0.2850	1.77	6.43***
CVD 505 Death in 4326 Men and 289 Deaths in 5442 Women						
Age	0.1113	1.86	11.46***	0.141	2.20	10.45***
Systolic BP	0.0099	1.28	3.49***	0.009	1.22	2.85**
Diastolic BP	0.0215	1.33	4.40***	0.016	1.23	2.75**
BMI	0.0174	1.08	1.13	-0.025	0.92	1.72
Serum Chol.	0.0034	1.15	2.54*	0.002	1.09	1.56
Blood Glucose	0.0037	1.10	2.32*	0.009	1.27	5.91***
Cig. Smoking£	0.3001	1.82	5.90***	0.397	2.21	6.15***
IHD 350 death in 4171 men and 168 Deaths in 5321 Women						
Age	0.095	1.70	8.57***	0.116	1.91	6.77***
Systolic BP	0.011	1.28	3.25**	0.014	1.41	4.80***
Diastolic BP	0.017	1.25	3.03**	0.008	1.11	1.05
BMI	0.016	1.05	0.90	0.002	1.01	0.09
Serum Choles.	0.004	1.16	2.79**	0.005	1.23	2.70**
Blood Glucose	0.003	1.08	1.72	0.011	1.32	5.92***
Cig. Smoking£	0.239	1.16	4.05***	0.323	1.91	3.91***
Stroke 79 death in 3900 men and 80 Death in 5232 Women						
Age	0.142	2.21	5.94***	0.150	2.31	6.24***
Systolic BP	0.015	1.40	2.42*	0.001	1.02	0.24
Diastolic BP	0.027	1.41	2.58*	0.044	1.79	5.25***
BMI	-0.005	0.98	-0.14	-0.084	0.69	-2.86**
Serum Choles.	0.001	1.04	0.24	-0.004	0.84	1.53
Blood Glucose	0.005	1.14	1.52	0.010	1.29	3.96***
Cig. Smoking£	0.355	2.03	2.97**	0.539	2.94	4.48***

@The approximate relative risk (standardized odds ratio) computed as the antilogarithm of the original coefficients for a change in the risk factor by an amount equal to its standard deviation.
£The odds ratio calculated for smokers and non-smokers.
*P<0.05, **P<0.01, ***P<0.001

TABLE 5.11. Missing Group Compared to Study Group, 10-14 Years All Causes, CVD, IHD and Stroke Mortality Rate and Possible CVD Risk Factors.

	Missing Group	Study Group	95% CI
MALE			
Numbers	2186	4783	-
Mean Age (Yr)	54.0	54.9***	0.64-1.18
Age-Adjusted Means£			
SBP (mmHg)	151.4***	147.7	2.51-4.89
DBP (mmHg)	87.2***	85.5	1.02-2.38
Schol.(mg/dl)	219.0	228.3***	7.11-11.49
BMI (Kg/m)	26.0***	25.7	0.13-0.47
% Smokers	55.6***	49.2	3.90-8.90
10-14 Year Age-Adjusted Overall Mortality Rate@	21.1 (444)*	19.8 (959)	
10-14 Years Age-Adjusted CVD Mortality Rate@	12.8 (248)**	11.3 (502)	
10-14 Years Age-adjusted IHD Mortality Rate@	10.0 (191)**	8.5 (371)	
10-14 Years Age-Adjusted Stroke Mortality Rate@	2.4 (40)	1.9 (80)	
FEMALE			
Numbers	2427	5812	-
Mean Age (Yr)	54.3	55.1***	0.54-1.18
Age-Adjusted Means£			
SBP (mmHg)	154.6***	148.6	4.77-7.23
DBP (mmHg)	86.4***	84.4	1.35-2.65
Schol.(mg/dl)	238.7	250.1***	8.88-13.92
BMI (Kg/m)	26.2***	25.6	0.38-0.82
% Smokers	45.5***	40.7	2.50-7.10
10-14 Year Age-Adjusted Overall Mortality Rate@	11.1 (289)	10.4 (655)	
10-14 Years Age-Adjusted CVD Mortality Rate@	5.5 (133)	4.8 (286)	
10-14 Years Age-adjusted IHD Mortality Rate@	3.8 (92)*	3.1 (181)	
10-14 Years Age-Adjusted Stroke Mortality Rate@	1.1 (25)	1.4 (80)	

£Age-adjusted of means by averaging 5-year age group.
*P<0.05, **P<0.01, ***P<0.001
@Number of death in Brackets, age-adjusted death rate per 1,000 person year of observation, adjusted by direct method by population of Scotland in 1981 for the four five year age group and differences tested by Mantel-Haenszel Chi-square test.

TABLE 5.12. Trends of Observed/Expected Ratio of Overall Causes of Deaths in Renfrew and Paisley, Scotland by Age and Gender, 1972-86.

Year	Age Group				All Ages
	54-54	55-64	65-74	75-84	
			Male		
1972	1.03	0.71	0.00	1.00	0.78
1973	0.80	0.98	0.00	1.00	0.82
1974	0.61	0.62	0.16	1.00	0.56
1975	0.47	0.58	0.65	1.00	0.58
1976	0.66	0.83	0.54	1.00	0.74
1977	1.10	0.65	0.70	1.00	0.74
1978	0.81	0.81	0.56	1.00	0.72
1979	1.32	0.99	0.72	1.00	0.91
1980	0.63	0.84	0.65	1.00	0.73
1981	1.12	0.70	0.64	1.00	0.69
1982	1.24	0.75	0.73	2.08	0.75
1983	0.83	0.87	0.76	0.54	0.80
1984	1.36	0.88	0.79	1.08	0.83
1985	0.00	0.64	0.66	0.53	0.65
1972-1986 Mean O/E	0.84	0.78	0.69	0.72	0.74
1977-86	1.05	0.79	0.69	1.02	0.76
			Female		
1972	0.30	0.30	0.00	1.00	0.28
1973	0.96	0.66	0.00	1.00	0.65
1974	0.71	0.74	0.64	1.00	0.72
1975	0.44	0.44	0.51	1.00	0.45
1976	0.50	0.62	0.80	1.00	0.63
1977	0.89	0.85	0.55	1.00	0.76
1978	1.22	0.65	0.57	1.00	0.69
1979	1.21	0.83	0.56	1.00	0.74
1980	1.16	0.69	0.71	1.00	0.73
1981	0.77	0.85	0.63	1.00	0.72
1982	0.88	0.52	0.68	0.00	0.62
1983	0.62	0.63	0.66	0.55	0.64
1984	1.91	0.82	0.85	0.27	0.81
1985	0.00	0.74	0.75	0.40	0.71
1972-1986 Mean O/E	0.82	0.70	0.68	0.38	0.69
1977-86	1.08	0.73	0.66	0.69	0.71

TABLE 5.13. Trends of Observed/Expected Ratio of Ischaemic Heart Disease Deaths in Renfrew and Paisley, Scotland by Age and Gender, 1972-86.

Year	Age Group				All Ages
	54-54	55-64	65-74	75-84	
			Male		
1972	1.52	1.48	0.00	1.00	1.44
1973	0.83	0.83	0.00	1.00	0.74
1974	1.09	0.75	0.00	1.00	0.76
1975	0.57	0.43	0.61	1.00	0.49
1976	0.69	1.06	0.42	1.00	0.86
1977	1.27	0.64	0.85	1.00	0.79
1978	0.79	0.92	0.68	1.00	0.82
1979	1.79	0.93	0.79	1.00	0.96
1980	0.80	0.90	0.49	1.00	0.70
1981	2.00	0.72	0.76	1.00	0.81
1982	0.52	0.71	0.74	0.49	0.73
1983	0.97	0.95	0.69	0.00	0.79
1984	3.29	0.90	0.76	0.45	0.81
1985	0.00	0.61	0.67	0.62	0.65
1972-1986 Mean O/E	1.03	0.81	0.69	0.59	0.78
1977-86	1.27	0.81	0.71	0.79	0.78
			Female		
1972	0.00	0.61	0.00	1.00	0.44
1973	0.00	0.00	0.00	1.00	0.00
1974	0.68	1.28	2.16	1.00	1.33
1975	0.00	0.29	0.33	1.00	0.25
1976	0.71	1.25	0.55	1.00	1.00
1977	1.20	0.71	0.54	1.00	0.70
1978	1.10	0.61	0.70	1.00	0.68
1979	0.63	0.84	0.57	1.00	0.68
1980	0.00	0.62	0.72	1.00	0.65
1981	3.85	0.88	0.94	1.00	0.98
1982	1.77	0.56	0.54	0.00	0.56
1983	4.44	0.84	0.63	1.01	0.72
1984	0.00	0.67	0.82	0.47	0.76
1985	0.00	0.90	0.83	0.20	0.78
1972-1986 Mean O/E	0.84	0.75	0.72	0.36	0.73
1977-86	1.44	0.74	0.70	0.74	0.72

TABLE 6.1. Diabetes at Baseline and 10-14 Years Age, Gender Adjusted Mortality Rate by Cause, in Men and Women.

Diabetes Status	Male		Female		Male/Female Relative Risk
	Mortality Rate@	Relative Risk	Mortality Rate@	Relative Risk	
All Causes					
Diabetics	19.6 (15)	0.99	35.3 (24)*	3.49	0.55
Non-diabetics	19.8 (945)	-	10.1 (631)	-	1.96
All	19.8 (960)	-	10.4 (635)	-	1.90
Cardiovascular Disease					
Diabetics	14.1 (10)	1.25	23.6 (14)**	5.13	0.60
Non-diabetics	11.2 (492)	-	4.6 (272)	-	2.43
All	11.3 (502)	-	4.8 (286)	-	2.35
Ischaemic Heart Disease					
Diabetics	12.7 (8)	1.51	14.0 (7) **	4.67	0.91
Non-diabetics	8.4 (362)	-	3.0 (174)	-	2.80
All	8.5 (370)	-	3.1 (181)	-	2.74
Stroke					
Diabetics	1.6 (1)	0.8	14.1 (7) **10.84		0.11
Non-diabetics	2.0 (79)	-	1.3 (73)	-	1.54
All	1.9 (80)	-	1.4 (80)	-	1.36

@Rate per 1000 person year of observation, adjusted by Scotland population 1981 for the four 5-year age group. The number of deaths are shown in brackets.
Mantel-Haenszel X^2 Test: *P<0.01, **P<0.001

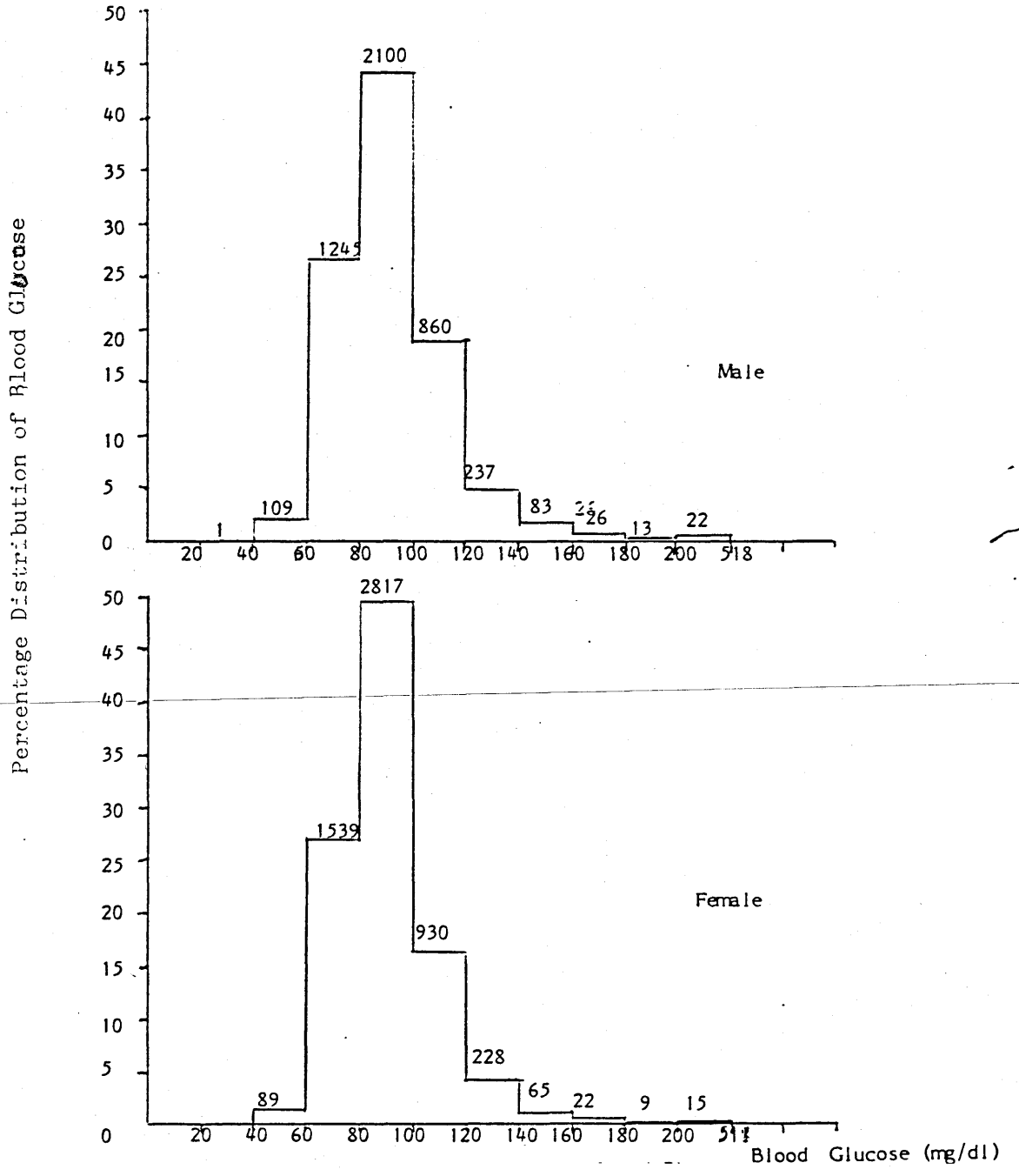


FIGURE 6.1. The Distribution of Casual Blood Glucose in Men and Women.

Table 6.2. Mean Values, Their Standard Deviations, Range and Simple Correlation Coefficients with Glucose at Baseline for 10410 Men and Women.

Variable	Mean and Standard Deviation			Range			Simple r with Blood Glucose@
	Male	Female	Total	Male	Female	Total	
Age (Yr)	55.0 (5.6)	55.0 (5.6)	55.0 (5.6)	45-65	45-65	45-65	0.0614***
Blood Glucose (mg/dl)	92.4 (24.5)	90.6 (21.1)	91.4 (22.7)	40-518	41-511	40-518	1.0000
Body Mass Index	25.7 (3.4)	25.6 (4.4)	25.7 (4.0)	14-48	14-68	14-68	0.0703***
Systolic BP (mmHg)	147.4 (22.4)	148.6 (22.9)	148.1 (23.8)	88-249	80-270	80-270	0.1217***
Diastolic BP (mmHg)	85.5 (13.1)	84.5 (13.2)	84.9 (13.2)	25-155	44-151	25-155	0.0334***
Serum Chol. (mmHg)	228.3 (37.3)	250.2 (42.1)	240.3 (41.4)	95-463	73-463	73-463	-0.0297***

@The simple correlation for both genders combined and separately was similar.
***P<0.001
The standard deviations are shown in brackets.
This table exclude known diabetics.

TABLE 6.3. Casual Blood Glucose Level According to Age and Gender.

Age (Yr)	Number		Blood Glucose (mg/dl)			
	Male	Female	Male		Female	
			Mean	SD	Mean	SD
45-49	1167	1355	90.6	23.2	88.1	17.0
50-54	1278	1536	92.3	22.2	89.4	20.8
55-59	1153	1434	93.1	28.0	91.8	22.3
60-64	1098	1389	93.7	24.5	93.0	23.4
Total	4696	5714	92.4	24.5	90.6	21.1

Differences is statistically significant Male: F=3.5 P<0.01, Linearity F=9.9, P<0.001 Female: F=15.4 P<0.0001, Linearity F=45.2, P<0.0001.

TABLE 6.4. Smoking Status at Baseline.

Smoking Categories	Number (%)			Casual Blood Glucose Mean and Standard Deviation		
	Male	Female	Total	Male	Female	Total
Never Smokers	994 (21.2)	2872 (50.3)	3866 (37.1)	94.5 (27.3)	91.7 (21.4)	92.4 (23.1)
Ex-smoker	1381 (29.4)	503 (8.8)	1884 (18.1)	93.2 (25.1)	91.1 (27.0)	92.6 (25.6)
Current Smokers	2321 (49.4)	2339 (40.9)	4660 (44.8)	91.1 (22.9)	89.1 (19.2)	90.1 (21.2)
<9 cigarette/day	309 (13.3)	606 (25.9)	915 (19.7)	92.3 (27.7)	88.2 (16.6)	89.6 (21.1)
10-19 Cigarette/day	1347 (58.1)	1516 (64.9)	2663 (61.5)	91.2 (23.4)	89.3 (20.1)	90.2 (21.8)
≥20 Cigarette/day	662 (28.5)	214 (9.2)	876 (18.8)	90.4 (19.2)	89.5 (19.0)	90.2 (19.1)
All	4696 (45.1)	5714 (54.9)	10410 (100)	92.3 (24.5)	90.5 (21.1)	91.3 (22.7)

TABLE 6.5. Smoking Habits by Quintiles and percentile of Casual Blood Glucose in Men and Women.

Quintiles of Blood Glucose	Blood Glucose Range (mg/dl)	Number	Prevalence Rate@ (No.) Current Smokers	Never Smokers	Ex-smokers
			Male		
1	40-76	991	53.3**(529)	18.1**(178)	60.9(277)
2	77-85	1036	51.2 (532)	20.1 (206)	58.7(294)
3	86-94	773	49.5 (382)	20.1 (155)	60.1(234)
4	95-103	883	46.9 (414)	23.3 (205)	56.1(262)
5	104-518	1013	46.1 (464)	23.1 (233)	57.9(314)
Highest 5%	130-518	280	44.2* (122)	23.3 (65)	59.1(94)
Lowest 5%	40-65	315	52.6 (165)	20.0 (58)	60.0(87)
Highest 2%	148-518	111	43.5 (47)	28.0 (32)	50.0(32)
Lowest 2%	40-59	154	48.8 (75)	24.6 (38)	51.9(41)
All	40-518	4696	49.4(2321)	21.4 (994)	29.4(1381)
			Female		
1	41-77	1143	44.7* (514)	46.5**(524)	15.6(97)
2	78-85	1451	41.7 (606)	48.5 (698)	16.8(140)
3	86-92	1075	43.3 (465)	48.8 (521)	13.3(80)
4	93-102	1025	38.7 (393)	52.1 (530)	14.4(89)
5	103-511	1020	37.5 (361)	52.8 (551)	15.0(97)
Highest 5%	122-511	218	42.5***(82)	50.9 (115)	12.9(17)
Lowest 5%	41-67	313	48.7 (153)	42.9 (133)	15.8(25)
Highest 2%	139-511	88	45.3 (35)	49.7* (48)	9.4(5)
Lowest 2%	41-61	114	53.6 (61)	37.0 (42)	20.7(11)
All	41-511	5714	40.9 (2339)	50.3 (2872)	8.8(503)

@Prevalence rate per 100 person, adjusted by Scotland population of 1981 of the four 5 year age groups.
This table excludes known diabetics.
Mantel-Haenszel chi-square Test: *P<0.05, **P<0.01, ***P<0.001 (bottom quintile, 5% and 2% compared with the corresponding upper quintile, 5% and 2%).

TABLE 6.6. Quintile, Highest and Lowest 5 and 2 Percent of Casual Blood Glucose Value and 10 to 14 Years Age-adjusted Mortality by Cause and Gender.

Quintile of Blood Glucose	No. of Subjects at Base-line	10-14 Year Age-adjusted Mortality Rate@							
		All Causes		CVD		IHD		Stroke	
		No.	Rate	No.	Rate	No.	Rate	No.	Rate
Male									
1	991	203	21.1	104	11.8	79	9.2	18	2.3
2	1036	186	18.1	98	10.4	69	7.5	18	2.0
3	773	170	21.8	83	11.7	66	9.5	12	1.8
4	883	171	18.2	92	10.5	64	7.4	13	1.6
5	1013	213	20.2	114	11.8	83	8.9	18	2.0
Highest 5%	280	65	22.2	39	14.4**	34	12.6**	3	1.4
Lowest 5%	315	55	18.0	20	7.3	15	5.6	4	1.6
Highest 2%	111	29	25.1	22	19.8**	18	16.6*	3	3.4
Lowest 2%	154	31	21.0	10	7.7	9	7.0	1	0.8
All	4696	943	19.8	491	11.2	361	8.4	79	2.0
Female									
1	1143	123	10.8	52	4.8	30	2.8	16	1.5
2	1451	126	8.1	58	3.9	36	2.4	15	1.1
3	1075	120	10.2	50	4.5	33	3.0	15	1.4
4	1025	122	10.4	48	4.3	27	2.4	16	1.4
5	1020	140	11.9	64	5.5	48	4.1	11	1.0
Highest 5%	218	40	15.1	18	6.8	12	4.8	5	1.9
Lowest 5%	313	31	9.9	13	4.5	7	2.5	6	2.2
Highest 2%	88	21	21.7*	13	12.6**	9	9.6	4	3.5
Lowest 2%	114	11	9.7	5	4.8	4	3.7	1	1.1
All	5714	631	10.1	272	4.6	174	3.0	73	1.3

Difference between quintile and percentile of blood glucose, Mantel-Haenszel chi-square Test: *P<0.05, **P<0.01, ***P<0.001.
Missing Cases=2
This table excludes known diabetics.
@Adjusted death rate per 1,000 person year of observation, adjusted by direct method to population of Scotland in 1981 for the four 5-year age groups.

TABLE 6.7. Univariate Analysis, Dichotomization of Baseline Variables and 10 to 14 Year Age, Gender Adjusted Mortality by Cause, in Men and Women.

Variable		No. of Subjects		10-14 Year Age-Adjusted Mortality Rate@					
				Male			Female		
		Male	Female	No. of Death	Death Rate	RR	No. of Death	Death Rate	RR
All Causes									
Blood Glucose	<126	4417	5500	880	19.7	-	591	9.9	-
	≥126	277	214	63	21.8	1.11	40	15.1	1.55
Systolic BP	<160	3534	4115	615	17.6	-	380	9.0	-
	≥160	1160	1599	328	25.4	1.44	251	12.5	1.39
Diastolic BP	<95	3739	4643	709	18.7	-	463	9.4	-
	≥95	955	1070	234	23.9	1.28	167	12.5	1.33
Serum Chol.	<250	3420	2926	715	20.0	-	321	10.7	-
	≥250	1274	2788	228	19.4	0.97	310	9.7	0.91
BMI	<27	3116	3891	643	20.4	-	407	9.9	-
	≥27	1578	1823	300	18.7	0.92	224	10.4	1.05
Use of Cigaret.	No	2374	3375	373	14.7	-	324	8.2	-
	yes	2320	2339	570	25.5	1.73	307	13.2	1.61
All		4694	5714	943	19.8	-	631	10.1	-
Cardiovascular Causes									
Blood Glucose	<126	3991	5153	454	11.1	-	254	4.4	-
	≥126	251	202	37	13.9	1.25	18	6.8	1.57
Systolic BP	<160	3215	3876	292	9.0	-	141	3.6	-
	≥160	1031	1479	199	16.7	1.85	131	6.5	1.80
Diastolic BP	<95	3367	4354	337	9.7	-	174	3.7	-
	≥95	875	1000	154	16.9	1.74	97	7.3	1.97
Serum Chol.	<250	3053	2722	348	10.6	-	117	4.4	-
	≥250	1189	2633	143	12.9	1.21	155	4.9	1.11
BMI	<27	2775	3652	302	10.6	-	168	4.3	-
	≥27	1467	1703	189	12.5	1.18	104	4.8	1.12
Use of Cigaret.	No	2219	3185	218	9.1	-	134	3.4	-
	Yes	2023	2170	273	13.8	1.51	138	6.4	1.88
All		4242	5355	491	11.2	-	272	4.6	-

TABLE 6.7.Continued

Variable		No. of Subjects		10-14 Year Age-Adjusted Mortality Rate@					
				Male			Female		
		Male	Female	No. of Death	Death Rate	RR	No. of Death	Death Rate	RR
Ischaemic Heart Disease									
Blood Glucose	<126	3866	5071	329	8.2	-	162	2.9	-
	⩾126	246	186	32	12.1	1.47	12	4.8	1.69
Systolic BP	<160	3143	3825	224	6.9	-	90	2.3	-
	⩾160	969	1432	137	12.2	1.77	84	4.2	1.83
Diastolic BP	<95	3283	4294	253	7.4	-	114	2.4	-
	⩾95	829	963	108	12.4	1.67	60	4.8	2.0
Serum Chol.	<250	2953	2677	248	7.8	-	72	2.6	-
	⩾250	1159	2580	113	10.3	1.32	102	3.3	1.27
BMI	<27	2692	3583	219	7.8	-	99	2.6	-
	⩾27	1420	1674	142	9.7	1.24	75	3.6	1.38
Use of Cigarette	No	2168	3142	167	7.1	-	91	2.3	-
	Yes	1944	2115	194	10.1	1.42	83	3.8	1.65
All		4112	5257	361	8.4	-	174	3.0	-
Cerebrovascular Causes									
Blood Glucose	<126	3613	4977	76	2.0	-	68	1.2	-
	⩾126	217	179	3	1.4	0.70	5	1.9	1.58
Systolic BP	<160	2959	3776	40	1.3	-	41	1.1	-
	⩾160	871	1380	39	3.7	2.85	32	1.7	1.54
Diastolic BP	<95	3078	4224	48	1.5	-	44	1.0	-
	⩾95	752	931	31	3.9	2.60	28	2.2	2.20
Serum Chol.	<250	2768	2640	63	1.8	-	35	1.3	-
	⩾250	1062	2514	16	2.1	1.17	38	1.2	0.92
BMI	<27	2522	3538	49	1.9	-	54	1.3	-
	⩾27	1308	1618	30	2.1	1.10	19	0.9	0.69
Use of Cigarette	No	2034	3078	33	1.5	-	27	0.7	-
	Yes	1796	2078	46	2.5	1.67	46	2.3	2.28
All		3830	5156	79	2.0	-	73	1.3	-

Units as in Table 6.2.
@Death rate per 1,000 person years of observation, age adjusted by direct method to 1981 Scotland population for the four 5-year age groups.
Missing cases=2
Known diabetics excluded.

TABLE 6.8. Ten to Fourteen Year Age, Adjusted Overall Mortality Rates by Degree of Casual Blood Glucose Concentration and Risk Factors Status in Men and Women.

Risk Factors		Normoglycaemic Groups		Asymptomatic Hyperglycaemic Group		Hyperglycaemic Normoglycaemic Mortality Rate Ratio
		Mortality Rate per 1,000£	RR (b/a)	Mortality Rate per 1,000£	RR (b/a)	
Male						
(a)S.Chol.	<250	20.0 (669)	1.0	21.3 (46)	1.1	1.1
(b)S.Chol.	≥250	19.2 (211)	-	23.2 (17)	-	1.2
(a)SBP	<160	17.5 (573)	1.4	18.5 (36)	1.7	1.0
(b)SBP	≥160	25.2 (301)	-	30.7 (27)	-	1.2
(a)DBP	<95	18.7 (664)	1.3	20.3 (45)	1.4	1.1
(b)DBP	≥95	23.7 (216)	-	29.1 (18)	-	1.2
(a)BMI	<27	20.4 (606)	0.9	21.0 (37)	1.1	1.0
(b)BMI	≥27	18.4 (274)	-	22.2 (26)	-	1.2
(a)Non-Smoker		14.6 (345)	1.7	17.0 (28)	1.7	1.2
(b)Smoker		25.4 (535)	-	29.2 (35)	-	1.0
Female						
(a)S.Chol.	<250	10.4 (298)	0.9	16.6 (23)	0.9	1.6
(b)S.Chol.	≥250	9.5 (293)	-	15.4 (17)	-	1.6
(a)SBP	<160	8.8 (361)	1.4	13.6 (19)	1.4	1.5
(b)SBP	≥160	12.0 (230)	-	19.8 (21)	-	1.6
(a)DBP	<95	9.2 (434)	1.3	14.8 (29)	1.2	1.6
(b)DBP	≥95	12.3 (156)	-	17.6 (11)	-	1.4
(a)BMI	<27	9.8 (385)	1.0	13.9 (22)	1.2	1.4
(b)BMI	≥27	10.0 (206)	-	16.8 (18)	-	1.7
(a)Non-Smoker		7.8 (296)	1.7	15.9 (28)	0.8	2.0
(b)Smoker		13.1 (295)	-	13.6 (12)	-	1.0

Units as in Table 6.2.
Known diabetics excluded.
‡Death rate per 1,000 person year of observation age-adjusted to 1981 Scottish population; numbers in parenthesis refer to number of deaths.
Asymptomatic hyperglycaemia defined as upper 5% of casual blood glucose distribution.

TABLE 6.9. Ten to Fourteen Year Age, Adjusted Cardiovascular Mortality Rates by Degree of Casual Blood Glucose Concentration and Risk Factors Status in Men and Women.

Risk Factors	Normoglycaemic Groups		Asymptomatic Hyperglycaemic Group		Hyperglycaemic Normoglycaemic Mortality Rate Ratio
	Mortality Rate per 1,000£	RR (b/a)	Mortality Rate per 1,000£	RR (b/a)	
Male					
(a)S.Chol.<250	10.5 (322)	1.2	13.1 (26)	1.3	1.2
(b)S.Chol.≥250	12.8 (132)	-	16.9 (11)	-	1.3
(a)SBP <160	8.8 (271)	1.9	11.4 (21)	1.5	1.3
(b)SBP ≥160	16.6 (183)	-	16.9 (16)	-	1.0
(a)DBP <95	9.5 (311)	1.8	12.9 (26)	1.4	1.3
(b)DBP ≥95	16.7 (143)	-	18.2 (11)	-	1.1
(a)BMI <27	10.5 (284)	1.2	11.3 (18)	1.5	1.1
(b)BMI ≥27	12.2 (170)	-	17.1 (19)	-	1.4
(a)Non-Smoker	8.9 (200)	1.5	11.4 (18)	1.5	1.3
(b)Smoker	13.6 (254)	-	17.4 (19)	-	1.3
Female					
(a)S.Chol.<250	4.0 (107)	1.2	7.7 (10)	0.8	1.9
(b)S.Chol.≥250	4.9 (147)	-	6.0 (8)	-	1.2
(a)SBP <160	3.5 (133)	1.8	5.6 (8)	1.5	1.6
(b)SBP ≥160	6.3 (121)	-	8.7 (10)	-	1.4
(a)DBP <95	3.6 (163)	2.0	5.8 (11)	2.1	1.6
(b)DBP ≥95	7.2 (90)	-	12.5 (7)	-	1.7
(a)BMI <27	4.3 (159)	1.1	5.6 (9)	1.5	1.3
(b)BMI ≥27	4.7 (95)	-	8.3 (9)	-	1.8
(a)Non-Smoker	3.3 (123)	1.9	6.4 (11)	1.3	1.9
(b)Smoker	6.2 (131)	-	8.3 (7)	-	1.3

Units as in Table 6.2.
Known diabetics excluded.
£Death rate per 1,000 person year of observation, age-adjusted to 1981 Scottish population; numbers in parenthesis refer to number of deaths.
Asymptomatic hyperglycaemia defined as upper 5% of casual blood glucose distribution.

TABLE 6.10. Ten to Fourteen Year Age, Adjusted Ischaemic Heart Disease Mortality Rates by Degree of Casual Blood Glucose Concentration and Risk Factors Status in Men and Women.

Risk Factors	Normoglycaemic Groups Group		Asymptomatic Hyperglycaemic		Hyper-glycaemic/ Normo-glycaemic
	Mortality Rate per 1,000£	RR (b/a)	Mortality Rate per 1,000£	RR (b/a)	Rate Ratio
Male					
(a)S.Chol.<250	7.6 (226)	1.3	11.1 (22)	1.4	1.5
(b)S.Chol.≥250	10.3 (103)	-	15.6 (10)	-	1.5
(a)SBP <160	6.8 (206)	1.8	9.9 (18)	1.5	1.4
(b)SBP ≥160	12.0 (123)	-	15.4 (14)	-	1.3
(a)DBP <95	7.2 (231)	1.7	11.5 (23)	1.3	1.6
(b)DBP ≥95	12.0 (98)	-	15.2 (9)	-	1.3
(a)BMI <27	6.1 (165)	1.9	10.8 (17)	1.3	1.8
(b)BMI ≥27	11.8 (164)	-	14.1 (15)	-	1.2
(a)Non-Smoker	6.9 (151)	1.4	10.2 (16)	1.4	1.5
(b)Smoker	9.8 (178)	-	14.7 (16)	-	1.5
Female					
(a)S.Chol.<250	2.8 (74)	1.1	4.0 (5)	1.5	1.4
(b)S.Chol.≥250	3.0 (88)	-	5.9 (7)	-	2.0
(a)SBP <160	2.0 (76)	2.4	3.0 (4)	2.4	1.5
(b)SBP ≥160	4.8 (86)	-	7.1 (8)	-	1.5
(a)DBP <95	2.1 (93)	2.8	4.9 (9)	1.7	2.3
(b)DBP ≥95	6.0 (69)	-	8.3 (3)	-	1.4
(a)BMI <27	2.5 (93)	1.4	3.9 (6)	1.5	1.6
(b)BMI ≥27	3.5 (69)	-	5.7 (6)	-	1.6
(a)Non-Smoker	2.3 (78)	1.6	4.4 (7)	1.4	1.9
(b)Smoker	3.7 (84)	-	6.0 (5)	-	1.6

Units as in Table 6.2.
Known diabetics excluded.
£Death rate per 1,000 person year of observation age-adjusted to 1981 Scottish population; numbers in parenthesis refer to number of deaths.
Asymptomatic hyperglycaemia defined as upper 5% of casual blood glucose distribution.

TABLE 6.11. Ten to Fourteen Year Age, Adjusted Cerebrovascular Disease Mortality Rates by Degree of Casual Blood Glucose Concentration and Risk Factor Status in Men and Women.

Risk Factors	Normoglycaemic Groups		Asymptomatic Hyperglycaemic Group		Hyperglycaemic/ Normoglycaemic Rate Ratio
	Mortality Rate per 1000£	RR (b/a)	Mortality Rate per 1000£	RR (b/a)	
Male					
(a)S.Chol.<250	2.1 (60)	0.9	1.8 (3)	0	0.8
(b)S.Chol.≥250	1.9 (16)	-	0.0 (0)	-	-
(a)SBP <160	1.3 (38)	2.9	1.3 (2)	0.7	1.0
(b)SBP ≥160	3.8 (38)	-	0.9 (1)	-	0.2
(a)DBP <95	1.6 (47)	2.4	0.7 (1)	6.1	0.4
(b)DBP ≥95	3.8 (29)	-	4.3 (2)	-	1.1
(a)BMI <27	1.9 (48)	1.2	0.6 (1)	4.0	0.3
(b)BMI ≥27	2.2 (28)	-	2.4 (2)	-	1.1
(a)Non-Smoker	1.6 (32)	1.6	0.6 (1)	3.7	0.4
(b)Smoker	2.6 (44)	-	2.2 (2)	-	0.8
Female					
(a)S.Chol.<250	1.2 (32)	1.1	1.5 (2)	1.5	1.2
(b)S.Chol.≥250	1.3 (36)	-	2.3 (3)	-	1.8
(a)SBP <160	1.0 (38)	1.6	1.3 (2)	2.0	1.3
(b)SBP ≥160	1.6 (30)	-	2.6 (3)	-	1.6
(a)DBP <95	0.9 (42)	2.3	0.6 (1)	8.3	0.6
(b)DBP ≥95	2.1 (25)	-	5.0 (4)	-	2.4
(a)BMI <27	1.4 (51)	0.6	2.0 (3)	0.9	1.4
(b)BMI ≥27	0.8 (17)	-	1.9 (2)	-	2.4
(a)Non-Smoker	0.7 (24)	3.1	1.7 (3)	1.6	2.4
(b)Smoker	2.2 (44)	-	2.8 (2)	-	1.3

Units as in Table 6.2.
Known diabetics excluded.
£Death rate per 1,000 person year of observation age-adjusted to 1981 Scottish population; numbers in parenthesis refer to number of deaths.
Asymptomatic hyperglycaemia defined as upper 5% of casual blood glucose distribution.

Table 6.12. Upper 5% of Blood Glucose Distribution, 10-14 Years All Causes, CVD, IHD and Stroke Mortality Rate and Possible CVD Risk Factors by Gender.

	Normoglycaemic Group$		Hyperglycaemic Group$	
	Male	Female	Male	Female
Numbers	4419	5500	277	214
Mean Age (Yr)	54.8	55.0	55.4	56.3***
Age Adjusted Means@				
Blood Glucose	88.4	88.0	155.1***	145.0***
Systolic BP	147.2	148.3	152.7***	153.8***
Diastolic BP	85.4	84.4	85.5	83.9
S.Cholest.	228.4	250.3	226.1	246.2
BMI	25.7	25.5	26.1*	25.8
% Current Smokers	49.8	41.1	43.7	37.4
10-14 Years Age-adjusted Overall Mortality Rate	19.7(880)	9.9(591)	21.8(63)	15.4(40)
10-14 Years Age-adjusted CVD Mortality Rate	11.1(454)	4.4(244)	13.9(37)	6.9(28)
10-14 Years Age-adjusted IHD Mortality Rate	8.2(329)	2.9(162)	12.1(32)	4.9(12)
10-14 Years Age-adjusted Stroke Mortality Rate	2.0(76)	1.2(68)	1.4(3)	1.9(5)

@Age adjusted of means by averaging 5-year age group.
*** P<0.001 *P<0.05
Number of death in brackets, age adjusted death rate per 1,000 person year of observation, adjusted by direct method to population of Scotland in 1981 for the four 5-year age groups.
The table excluded known diabetics.
$Hyperglycaemics: upper 5% distribution of casual blood glucose value, ≥126 mg/dl; normoglycaemics: casual blood glucose value <126 mg/dl.

TABLE 6.13. Multiple Logistic Analysis of the Relationship Between Eight Variables and 10-14 Year Mortality by Cause.

Variable`	Logistic Coefficient	Odds Ratio@	Z-Test	Non Event		Event	
				Mean	SD	Mean	SD
All Causes 1582 Deaths in 10472 Men and Women							
Blood Glucose	0.006	1.09	3.8***	90.9	21.0	94.3	30.7
Gender	0.336	1.96	11.1***	-	-	-	-
Age	0.104	1.79	18.6***	54.5	5.5	57.5	5.1
Systolic BP	0.007	1.18	4.6***	146.9	23.2	154.6	26.0
Diastolic BP	0.009	1.13	3.1**	84.5	12.9	87.2	14.3
BMI	-0.022	0.92	2.8**	25.7	3.9	25.5	4.1
Serum Choles.	-0.002	0.92	2.2*	241.3	41.1	235.5	43.2
Smoking Habit	0.315	1.88	10.6***	-	-	-	-
Cardiovascular Disease 769 Deaths in 9652 Men and Women							
Blood Glucose	0.005	1.12	4.1***	90.9	21.0	96.1	37.3
Gender	0.514	2.79	11.9***	-	-	-	-
Age	0.118	1.94	14.9***	54.5	5.5	57.9	4.9
Systolic BP	0.010	1.27	4.5***	146.9	23.2	159.6	26.1
Diastolic BP	0.020	1.30	5.2***	84.5	12.9	90.4	14.1
BMI	-0.006	0.98	0.6	25.7	3.9	26.1	4.1
Serum Choles.	0.003	1.13	3.2**	241.3	41.1	242.3	43.2
Smoking Habit	0.342	1.98	8.4***	-	-	-	-
Ischaemic Heart Disease 502 Deaths in 9385 Men and Women							
Blood Glucose	0.006	1.14	4.0***	90.9	21.0	96.2	35.6
Gender	0.616	3.42	11.5***	-	-	-	-
Age	0.099	1.72	10.6***	54.5	5.5	57.5	5.0
Systolic BP	0.011	1.29	4.2***	146.9	23.2	158.7	25.6
Diastolic BP	0.015	1.21	3.2**	84.5	12.9	89.8	13.6
BMI	0.005	1.02	0.4	25.7	3.9	26.3	4.2
Serum Choles.	0.005	1.23	4.0***	241.3	41.1	243.8	43.2
Smoking Habit	0.276	1.74	5.7***	-	-	-	-
Stroke 151 Deaths in 9034 Men and Women							
Blood Glucose	0.007	1.16	2.9**	90.9	21.0	96.6	48.4
Gender	0.184	1.94	2.2*	-	-	-	-
Age	0.150	2.28	8.7***	54.5	5.5	58.6	4.7
Systolic BP	0.007	1.18	1.7	146.9	23.2	161.6	27.7
Diastolic BP	0.046	1.82	7.9***	84.5	12.9	92.3	16.4
BMI	-0.055	0.81	2.4*	25.7	3.9	25.5	3.9
Serum Choles.	0.001	1.04	0.5	241.3	41.1	239.8	44.0
Smoking Habit	0.472	2.57	5.5***	-	-	-	-

Units as in Table 6.2.
This table excludes known diabetics and cases with incomplete data.
Logistic coefficient estimated via maximum likelihood.
@The approximate relative risk (odds ratio) for a change in the risk factor by an amount equal to its standard deviation.
Abbreviation: BP=Blood Pressure, Choles.=cholesterol.
***P<0.0001 **P<0.01 *P<0.05

TABLE 6.14. Multiple Logistic Analysis of the Relationship Between Eight Variables and 10-14 Year Mortality by Cause, and Normoglycaemic and Hyperglycaemic group.

	Normoglycaemic Group			Hyperglycaemic Group		
Variable£	Logistic Coefficient	Odds Ratio@	Z-Test	Logistic Coefficient	Odds Ratio@	Z-Test
All Causes 1479 Death in 9942 Men and Women				**All Causes 110 Death in 530 Men and Women**		
Blood Glucose	0.0024	1.03	1.2	0.0060	1.32	2.9**
Gender	0.3506	2.02	11.7***	0.1487	1.35	1.3
Age	0.1046	1.80	18.2***	0.0901	1.65	4.1***
Systolic BP	0.0074	1.19	4.5***	0.0106	1.30	2.3*
Diastolic BP	0.0090	1.12	3.0**	0.0012	1.02	0.1
BMI	-0.0205	0.92	-2.5**	-0.0354	0.86	-1.2
Serum Choles.	-0.0016	0.94	-2.1*	-0.0019	0.92	-0.7
Smoking Habit	0.3185	1.89	10.4***	0.2617	1.69	2.5*
CVD 711 Death in 9174 Men and Women				**CVD 58 Death in 478 Men and Women**		
Blood Glucose	0.0024	1.03	0.8	0.0087	1.52	3.8***
Gender	0.5263	2.86	11.7***	0.3437	1.99	2.1*
Age	0.1176	1.91	14.4***	0.1261	2.03	4.2***
Systolic BP	0.0105	1.28	4.7***	0.0094	1.26	1.3
Diastolic BP	0.0187	1.28	4.7***	0.0294	1.48	2.6**
BMI	-0.0074	0.97	-0.7	0.0100	1.04	0.3
Serum Choles.	0.0032	1.14	3.1**	0.0023	1.10	0.6
Smoking Habit	0.3363	1.96	8.0***	0.3335	1.94	2.1*
IHD 457 Death in 8920 Men and Women				**IHD 45 Death in 465 Men and Women**		
Blood Glucose	0.0029	1.04	0.8	0.0078	1.41	3.0**
Gender	0.6246	3.49	11.2***	0.4366	2.39	2.4*
Age	0.0994	1.73	10.3***	0.0966	1.72	3.0***
Systolic BP	0.0105	1.28	3.8***	0.0176	1.55	2.7**
Diastolic BP	0.0159	1.23	3.3**	0.0074	1.10	0.4
BMI	0.0044	1.02	0.3	0.0078	1.03	0.2
Serum Choles.	0.0046	1.21	3.7***	0.0051	1.23	1.2
Smoking Habit	0.2632	1.69	5.2***	0.3568	2.04	2.1*
Stroke 143 Death in 8606 Men and Women				**Stroke 8 Deaths in 428 Men and Women**		
Blood Glucose	-0.0016	0.98	0.3	0.0175	2.17	3.8***
Gender	0.2323	1.59	2.7**	-0.4986	0.39	-1.0
Age	0.1390	2.15	7.8***	0.3256	6.40	2.5**
Systolic BP	0.0107	1.28	2.2*	-0.0081	0.81	-0.4
Diastolic BP	0.0313	1.50	3.9***	0.1000	3.78	2.9**
BMI	-0.0556	0.80	-2.3*	-0.0672	0.75	-0.6
Serum Choles.	-0.0002	0.99	0.0	-0.0238	0.38	-1.8*
Smoking Habit	0.4537	2.48	5.0***	0.6827	3.91	1.5

This table excludes known diabetics and cases with incomplete data.
Logistic Coefficient estimated via maximum likelihood.
@The approximate relative risk (odds ratio) for a change in the risk factor by an amount equal to its standard deviation.
Abbreviation: BP=Blood Pressure, Choles.=cholesterol.
*P<0.001, ***P<0.05.

TABLE 7.1.10-14 Year Age, Gender Adjusted Mortality and Age-Adjusted Relative Risk of Asymptomatic Hyperglycaemia Compared to Euglycaemia by Cause of Death, in Men and Women.

Variable	No. of Subjects		10-14 Year Age-Adjusted Mortality Rate						
	Male	Female	Male			Female			Gender Ratio
			No.	Rate	RR	No.	Rate	RR	
All Causes									
Normogly.	4417	5500	880	19.7	-	591	9.9	-	2.00
Hypergly.	277	214	63	21.8	1.11	40	15.4	1.55	1.41
Cardiovascular Disease									
Normogly.	3991	5153	454	11.1	-	244	4.4	-	2.52
Hypergly.	251	202	37	13.9	1.25	28	6.9	1.57	2.01
Ischaemic Heart Disease									
Normogly.	3866	5071	329	8.2	-	162	2.9	-	2.83
Hypergly.	246	186	32	12.1	1.47	12	4.9	1.69	2.47
Cerebrovascular Disease									
Normogly.	3613	4977	76	2.0	-	68	1.2	-	1.67
hypergly.	217	179	3	1.4	0.70	5	1.9	1.58	0.74

Death rate per 1,000 person year of observation, age-adjusted to 1981 Scottish population by four 5-year age groups.
Known diabetics excluded.
Abbreviation: Normogly.=Normoglycaemia, Hypergly.=Asymptomatic hyperglycaemia, RR=Relative Risk.

TABLE 7.2. Percentage of Hypertension (≥160 mmHg Systolic or ≥95 mmHg Diastolic) Cigarette Smoking, Serum Cholesterol Level (≥250 mg/dl) and BMI (≥27 Kg/m2) Among Asymptomatic Hyperglycaemic and Euglycaemic Men and Women.

Variables (High Risk Categories)	Male				Female			
	Hyper-glycaemics		Normo-glycaemics		Hyper-glycaemics		Normo-glycaemics	
	No	%	No	%	No	%	No	%
Systolic BP ≥160 mmHg	88	31.8**	1073	24.3	91	42.5**	1508	27.4
Diastolic BP ≥95 mmHg	63	22.7	892	20.2	47	22.0	1023	18.6
Serum Chol. ≥250 mg/d	70	25.3	1206	27.3	97	45.3	691	48.9
BMI ≥27	109	39.4*	1470	33.3	80	37.4	1743	31.7
Cigarette Smokers	121	43.7	2200	49.8*	80	37.4	2259	41.1

The difference between hyperglycaemics versus Normoglycaemics: *P<0.05, **P<0.01.

TABLE 7.3. Univariate and Bivariate Logistic Analysis of Overall Causes, CVD, IHD and Stroke Mortality for Blood Glucose in 10-14 Years of Follow-up for Men and Women.

Cause of Death	Male				Female			
	Logistic Coefficient@		Z-Test		Logistic Coefficient@		Z-Test	
	Crude	Age-Adjusted	Crude	Age-Adjusted	Crude	Age-Adjusted	Crude	Age-Adjusted
All	0.0029	0.0021	2.1*	1.5	0.0083	0.0068	5.0***	4.1***
CVD	0.0047	0.0041	2.9**	2.5*	0.0097	0.0083	4.7***	4.1***
IHD	0.0046	0.0041	2.3*	2.0*	0.0119	0.0109	4.8***	4.6***
Stroke	0.0056	0.0050	1.9*	1.5	0.0097	0.0078	2.6**	2.0*

This table exclude known diabetics and cases with incomplete data.
@Logistic coefficient estimated via maximum likelihood.
*P<0.05, **P<0.01, ***P<0.001

TABLE 7.4. Multiple Logistic Coefficients and Standardised Odds Ratio of Seven Cardiovascular Risk Factors and 10-14 Year Mortality by Cause and Gender.

Variables	Male			Female		
	Logistic Coefficient	Odds Ratio£	Z-Test	Logistic Coefficient	Odds Ratio£	Z-Test
All Causes 951 Males and 638 Females Deaths in 4724 Men and 5748 Women						
Age	0.1065	1.81	14.5***	0.1005	1.75	11.6***
Systolic BP	0.0071	1.17	3.2**	0.0095	1.26	5.3***
Diastolic BP	0.0109	1.12	2.8**	0.0045	1.06	1.0
BMI	-0.0154	0.95	-1.3	-0.0239	0.90	-2.3*
Serum Chol.	-0.0018	0.93	-1.8	-0.0016	0.93	-1.5
Blood Glucose	0.0021	1.05	1.5	0.0067	1.15	4.0***
Smoking@	0.3538	2.03	9.0***	0.2839	1.76	6.3***
Cardiovascular Disease 494 Male and 275 Female Deaths in 4267 Men and 5385 Women						
Age	0.1104	1.85	11.5***	0.1367	2.15	10.0***
Systolic BP	0.0101	1.25	3.5***	0.0095	1.26	2.9**
Diastolic BP	0.0209	1.31	4.2***	0.0168	1.25	2.8**
BMI	0.0182	1.06	1.2	0.0277	1.12	1.8
Serum Chol.	0.0034	1.13	2.6**	0.0026	1.11	1.7
Blood Glucose	0.0040	1.10	2.3**	0.0075	1.17	3.6***
Smoking@	0.3023	1.83	5.9***	0.4079	2.26	6.2***
Ischaemic Heart Disease 341 Male and 161 Female Deaths in 4114 Men and 5271 Women						
Age	0.0930	1.67	8.3***	0.1116	1.85	6.5***
Systolic BP	0.0108	1.27	3.3**	0.0152	1.45	4.9***
Diastolic BP	0.0165	1.23	2.8**	0.0094	1.13	1.2
BMI	0.0160	1.05	0.9	-0.0055	0.98	0.3
Serum Chol.	0.0045	1.18	2.9**	0.0047	1.22	2.5**
Blood Glucose	0.0037	1.09	1.8	0.0095	1.21	3.7***
Smoking@	0.2347	1.60	4.0***	0.3314	1.94	4.0***
Stroke 78 Male and 73 Female Deaths in 3851 Men and 5183 Women						
Age	0.1462	2.23	6.1***	0.1453	2.22	5.7***
Systolic BP	0.0152	1.39	2.4*	0.0019	1.05	0.3
Diastolic BP	0.0275	1.42	2.6**	0.0454	1.81	5.2***
BMI	-0.0037	0.99	-0.1	-0.0886	0.68	-2.8**
Serum Chol.	0.0002	1.03	0.2	-0.0028	0.89	-0.9
Blood Glucose	0.0050	1.13	1.4	0.0095	1.20	2.4**
Smoking@	0.3652	2.07	3.0***	0.5739	3.15	4.5***

This table excludes known diabetics and cases with incomplete data.
Logistic coefficient estimated via maximum likelihood.
£The approximate relative risk (odds ratio) for a change in the risk factor by an amount equal to its standard deviation.
@The odds ratios were calculated for smoker and non-smokers.
Abbreviation: BP=Blood Pressure, Choles.=cholesterol.
*P<0.05, **P<0.01, ***P<0.001.

TABLE 8.1. Mortality and Casual Blood Glucose Level by Quintile of Body Mass Index, in Males and Females.

	Quintile of Body Mass Index				
	1	2	3	4	5
Male					
No. of Subjects at Baseline	940	939	935	953	929
Total No. of Death	228	174	187	167	187**
All Death Rate@	23.8	18.5	19.9	16.7	20.3
Mortality Rate Ratio$	1.00	0.77	0.84	0.70	0.85
No. of CVD Deaths	90	80	100	96	125*
CVD Death Rate@	10.7	9.2	11.6	10.2	14.4
Mortality Rate Ratio$	1.00	0.86	1.08	0.95	1.34
No. of IHD Deaths	67	62	66	66	100**
IHD Death Rate@	8.1	7.4	7.9	7.2	11.8
Mortality Rate Ratio$	1.00	0.91	0.97	0.89	1.45
No. of CVA Deaths	14	10	20	18	17
CVA Death Rate@	1.8	1.2	2.6	2.1	2.1
Mortality Rate Ratio$	1.00	0.66	1.44	1.16	1.16
Mean Blood Glucose (SD)	91.2 (21.8)	90.7 (19.3)	91.2 (21.5)	92.3 (26.4)	96.4* (31.4)
Prevalence of Hyperglycaemia£	5.5%	5.4%	4.9%	6.1%	7.8%*
Female					
No. of Subjects at Baseline	1148	1149	1137	1146	1134
Total No. of Death	156	104	102	122	147***
All Death Rate@	13.2	8.8	8.3	8.6	11.1
Mortality Rate Ratio$	1.00	0.66	0.63	0.65	0.84
No. of CVD Deaths	67	35	42	59	69***
CVD Death Rate@	6.0	3.1	3.6	4.7	5.1
Mortality Rate Ratio$	1.00	0.52	0.60	0.78	0.85
No. of IHD Deaths	40	17	28	42	47***
IHD Death Rate@	3.6	1.4	2.4	3.4	3.6
Mortality Rate Ratio$	1.00	0.38	0.67	0.94	1.00
No. of CVA Deaths	21	15	10	14	13
CVA Death Rate@	1.9	1.4	0.9	1.1	1.0
Mortality Rate Ratio$	1.00	0.73	0.47	0.58	0.53
Mean Blood Glucose (SD)	89.4 (18.7)	89.7 (17.4)	90.1 (19.6)	90.2 (19.6)	93.4* (26.7)
Prevalence of Hyperglycaemia£	4.1%	3.5%	2.9%	3.1%	5.5%*

Differences between quintiles of BMI *P<0.05, **P<0.01, ***P<0.001

£Hyperglycaemia defined as upper 5% of casual blood glucose distribution, greater than 126 mg/dl.

The standard deviation of means shown in brackets.

@Death rate per 1000 person years of observation, age adjusted to 1981 Scottish population.

$Age adjusted mortality rate ratios for each of the higher quintiles were relative to age-adjusted mortality rate in the lowest quintile.

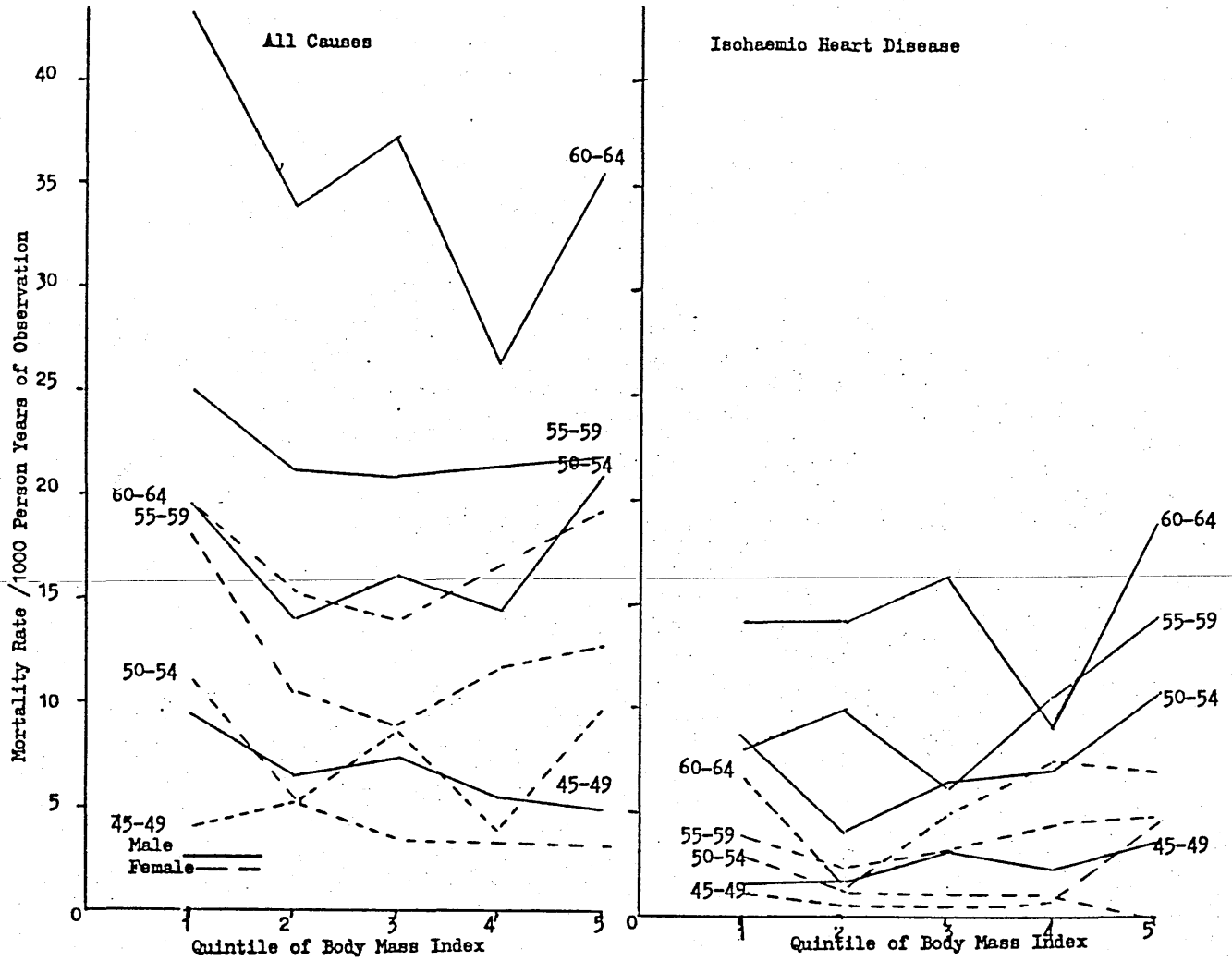


FIGURE 8.1. All Causes and Ischaemic Heart Disease Mortality Analysed by Body Mass Index Quintiles and Five Year Age Group For Males and Females.

TABLE 8.2. Total Deaths, CVD Deaths, IHD Deaths and CVA Deaths in Normoglycaemic and Hyperglycaemic Individuals by Quintile of BMI, in Males and Females.

	Male					Female				
	Quintile of BMI					Quintile of BMI				
	1	2	3	4	5	1	2	3	4	5
Overall Causes Deaths										
Normoglycaemics:										
No. of Deaths	219	162	175	156	168	145	100	96	118	132
Age-Adjusted Death Rate	24.0	18.2	19.8	16.7	18.5	12.8	8.9	8.0	9.2	10.4
Hyperglycaemics:£										
No.of deaths	9	12	12	11	19	11	4	6	4	15
Age-Adjusted Death Rate	19.4	24.2	21.3	18.2	25.6	23.7	9.0	14.2	9.0	18.7
Relative Risk@	0.8	1.3	1.1	1.1	1.4	1.8	1.0	1.8	1.0	1.8
Cardiovascular Disease Deaths										
Normoglycaemics:										
No. of Deaths	87	74	94	87	112	62	35	39	58	60
Age-Adjusted Death Rate	10.8	9.0	11.6	10.0	14.1	5.8	3.2	3.4	4.8	4.7
Hyperglycaemics:£										
No. of Deaths	3	6	6	9	13	5	0	3	1	9
Age-Adjusted Death Rate	8.4	14.0	13.1	15.6	19.3	9.6	0	7.9	4.1	10.4
Relative Risk@	0.8	1.5	1.1	1.6	1.4	1.6	0	2.3	0.8	2.2
Ischaemic Heart Disease Deaths										
Normoglycaemics:										
No. of Deaths	64	56	61	58	90	37	17	25	42	41
Age-Adjusted Death Rate	8.1	7.0	7.8	6.8	11.6	3.5	1.5	2.2	3.5	3.3
Hyperglycaemics:£										
No. of Deaths	3	6	5	8	10	3	0	3	0	6
Age-adjusted Death Rate	8.4	14.0	11.9	14.1	14.8	5.1	0	7.9	0	7.4
Relative Risk@	1.0	2.0	1.5	2.1	1.3	1.4	0	3.6	0	2.2
Cerebrovascular Accident Deaths										
Normoglycaemics:										
No. of Deaths	14	10	19	17	16	19	15	10	13	11
Age-Adjusted Death Rate	1.9	1.3	2.6	2.1	2.2	1.8	1.5	0.9	1.1	0.9
Hyperglycaemics:£										
No. of Deaths	0	0	1	1	1	2	0	0	1	2
Age-adjusted Death Rate	0	0	1.5	1.9	2.1	4.4	0	0	4.1	2.3
Relative Risk@	0	0	0.6	0.9	0.9	2.4	0	0	3.7	2.5

@Ratio of the age-adjusted death rates in hyperglycaemics and normoglycaemics.
£Hyperglycaemia defined as upper 5% of casual blood glucose distribution, greater than 126 mg/dl.
Death rate per 1,000 person years of observation, age adjusted to 1981 Scottish population.

Table 9.1. Age Specific and Adjusted Death Rates and gender Differential Among Men and Women.

Age (Year)	No. of Subjects		Death Rate@											
			All Causes			CVD			IHD			Stroke		
	M	F	M	F	M/F Ratio	M	F	M/F Ratio	M	F	M/F Ratio	M	F	M/F Ratio
45-49	1167	1355	6.8	3.9	1.7	3.1	1.2	2.6	2.6	0.7	3.7	0.2	0.4	0.5
50-54	1278	1536	17.1	7.4	2.3	9.2	2.5	3.7	7.5	1.9	3.9	1.2	0.6	2.0
55-59	1153	1434	22.1	12.5	1.8	13.6	5.7	2.4	10.0	3.8	2.6	3.2	1.3	2.5
60-64	1098	1385	35.1	17.7	2.0	20.0	9.6	2.1	14.3	5.8	2.5	3.5	3.0	1.2
Total	4696	5714												
Crude Rate			19.4	10.2	1.9	10.8	4.6	2.3	8.1	3.0	2.7	1.8	1.3	1.4
Age-Adjusted Death Rate			19.8	10.1	2.0	11.2	4.6	2.4	8.4	3.0	2.8	2.0	1.3	1.5

@Age specific and adjusted death rates per 1,000 person years of observation, adjusted by direct method by population of Scotland in 1981 for the four 5-year age groups.

TABLE 9.2. Differences in the Distribution of Risk Factors Among Men and Women.

Variables (High Risk Category)	Percentage and Number in High Risk Category				P*
	Male		Female		
	Number	Percentage	Number	Percentage	
Age 55-64 Years	2251	47.9	2823	49.4	NS
Blood Glucose≥126	277	5.9	214	3.7	P<0.001
Systolic BP≥160	1160	24.7	1599	28.0	P<0.001
Diastolic BP≥95	955	20.3	1070	18.7	P<0.05
Serum Choles.≥250	1274	27.1	2788	48.8	P<0.001
BMI≥27	1578	33.6	2339	31.9	NS
Cigarette Smoker	2320	49.4	2339	40.9	P<0.001

*Test of the difference in the distribution of risk factors among males and females.
NS, not significant.

TABLE 9.3. Univariate Analysis, Dichotomisation of Baseline Variables and 10 to 14 Year Age, Gender Adjusted Mortality and Gender Differential by Cause, in Men and Women.

Variable		No. of Subjects		10-14 Year Age-adjusted Mortality Rate				
				Male		Female		Male/Female Rate Ratio
		Male	Female	No. of Death	Rate	No. of Death	Rate	
All Causes								
Blood	<126	4417	5500	880	19.7	591	9.9	2.0
Glucose	≥126	277	214	63	21.8	40	15.1**	1.4
Systolic	<160	3534	4115	615	17.6	380	9.0	1.9
Pressure	≥160	1160	1599	328	25.4***	251	12.5***	2.0
Diastolic	<95	3739	4643	709	18.7	463	9.4	2.0
Pressure	≥95	955	1070	234	23.9***	167	12.5***	1.9
Serum	<250	3420	2926	715	20.0	321	10.7	1.9
Cholest.	≥250	1274	2788	228	19.4	310	9.7	2.0
BMI	<27	3116	3891	643	20.4	407	9.9	2.1
	≥27	1578	1823	300	18.7	224	10.4	1.8
Use of	No	2374	3375	373	14.7	324	8.2	1.8
Cigarette	Yes	2320	2339	570	25.5**	307	13.2**	1.9
All		4694	5714	943	19.8	631	10.1	2.0
Cardiovascular Causes								
Blood	<126	3991	5153	454	11.1	254	4.4	2.5
Glucose	≥126	251	202	37	13.9*	18	6.8	2.0
Systolic	<160	3215	3876	292	9.0	141	3.6	2.5
Pressure	≥160	1031	1479	199	16.7***	131	6.5***	2.6
Diastolic	<95	3367	4354	337	9.7	174	3.7	2.6
Pressure	≥95	875	1000	154	16.***	97	7.3**	2.3
Serum	<250	3053	2722	348	10.6	117	4.4	2.4
Cholest.	≥250	1189	2633	143	12.9	155	4.9	2.6
BMI	<27	2775	3652	302	10.6	168	4.3	2.5
	≥27	1467	1703	189	12.5	104	4.8	2.6
Use of	No	2219	3185	218	9.1	134	3.4	2.7
Cigarette	Yes	2023	2170	273	13.8***	138	6.4***	2.1
All		4242	5355	491	11.2	272	4.6	2.4

TABLE 9.3.Continued

Variable		No. of Subjects		10-14 Year Age-adjusted Mortality Rate				
				Male		Female		Male/Female Rate Ratio
		Male	Female	No. of Death	Rate	No. of Death	Rate	
Ischaemic Heart Disease								
Blood	<126	3866	5071	329	8.2	162	2.9	2.8
Glucose	≥126	246	186	32	12.1*	12	4.8	2.5
Systolic	<160	3143	3825	224	6.9	90	2.3	3.0
Pressure	≥160	969	1432	137	12.2***	84	4.2***	2.9
Diastolic	<95	3283	4294	253	7.4	114	2.4	3.1
Pressure	≥95	829	963	108	12.4***	60	4.8***	2.6
Serum	<250	2953	2677	248	7.8	72	2.6	3.0
Cholest.	≥250	1159	2580	113	10.3	102	3.3	3.1
BMI	<27	2692	3583	219	7.8	99	2.6	3.0
	≥27	1420	1674	142	9.7	75	3.6*	2.7
Use of	No	2168	3142	167	7.1	91	2.3	3.1
Cigarette	Yes	1944	2115	194	10.1	83	3.8***	2.6
All		4112	5257	361	8.4	174	3.0	2.8
Cerebrovascular Causes								
Blood	<126	3613	4977	76	2.0	68	1.2	1.7
Glucose	≥126	217	179	3	1.4	5	1.9	0.7
Systolic	<160	2959	3776	40	1.3	41	1.1	1.2
Pressure	≥160	871	1380	39	3.7***	32	1.7	2.2
Diastolic	<95	3078	4224	48	1.5	44	1.0	1.5
Pressure	≥95	752	931	31	3.9***	28	2.2***	1.8
Serum	<250	2768	2640	63	1.8	35	1.3	1.4
Cholest.	≥250	1062	2514	16	2.1	38	1.2	1.7
BMI	<27	2522	3538	49	1.9	54	1.3	1.5
	≥27	1308	1618	30	2.1	19	0.9	2.3
Use of	No	2034	3078	33	1.5	27	0.7	2.1
Cigarette	Yes	1796	2078	46	2.5*	46	2.3***	1.1
All		3830	5156	79	2.0	73	1.3	1.5

Death rate per 1,000 person years of observation, age adjusted by direct method to 1981 Scotland population for the four 5-year age groups.
Missing cases=2
Known diabetics excluded.
Significantly different from low risk category *P<0.05, **P<0.01, ***P<0.001. .PA

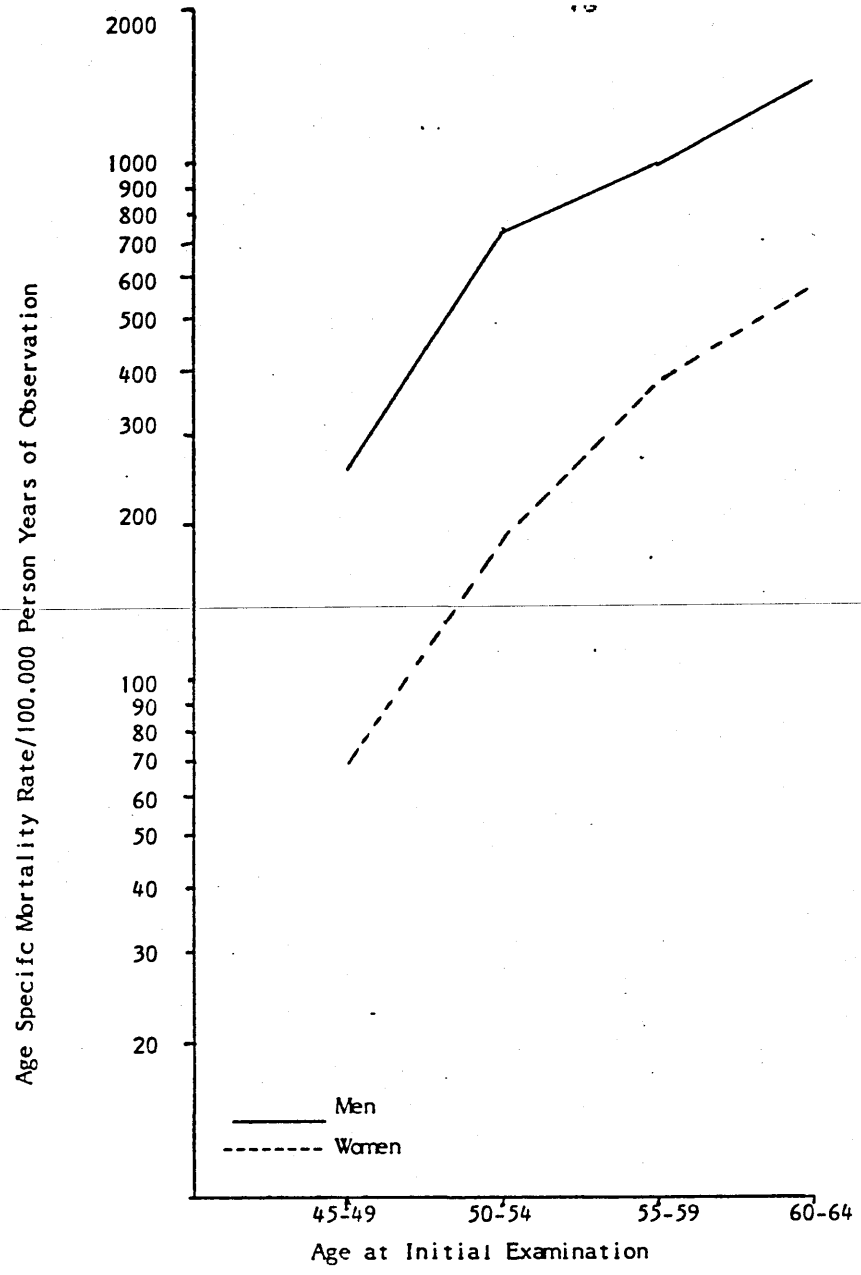


FIGURE 10.1. Mortality Rate of Ischaemic Heart Disease by Age and Gender.

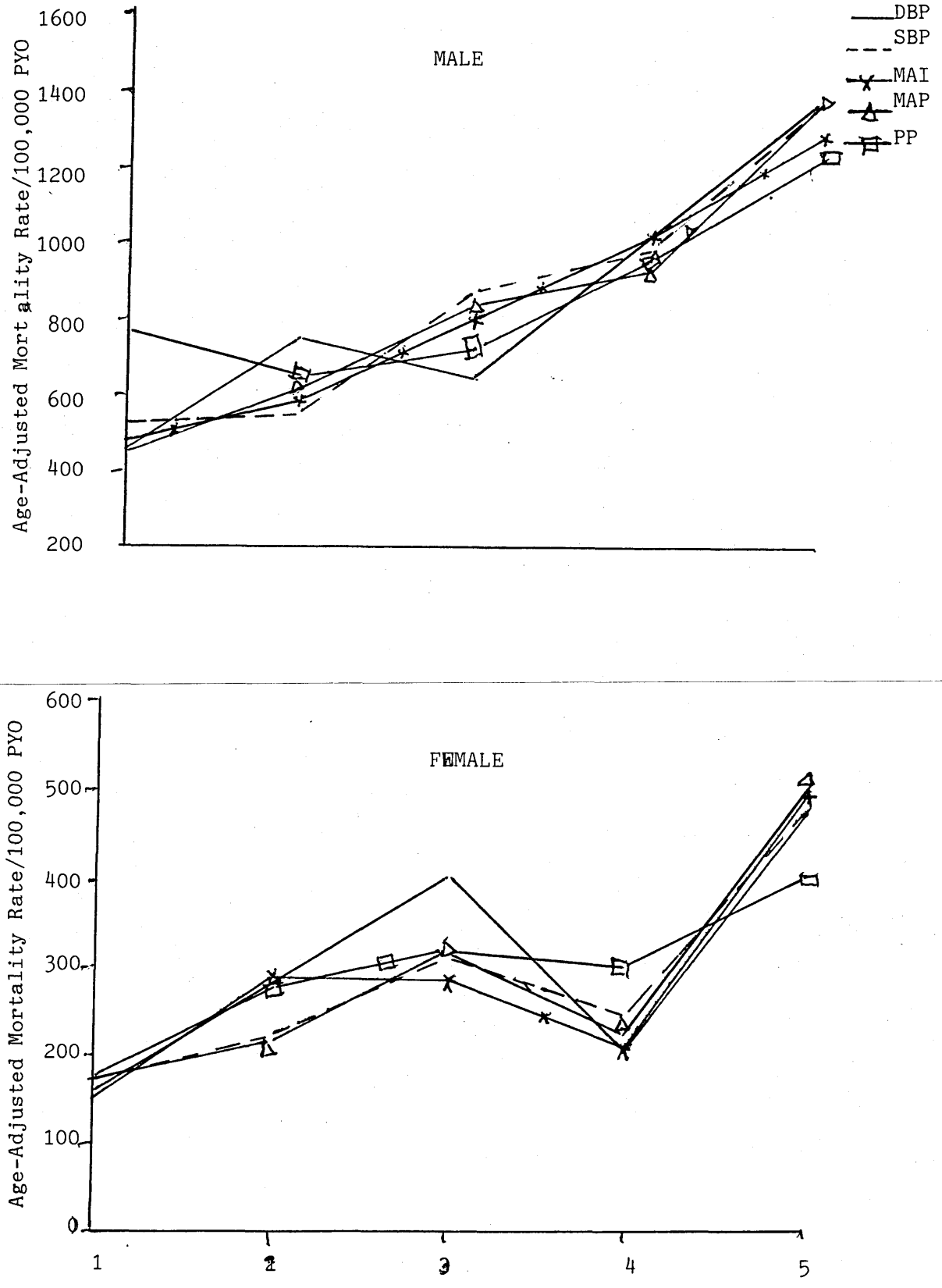


FIGURE 10.2. Ten to Fourteen Years Age-Adjusted Mortality Rate of Ischaemic Heart Disease According to Systolic and Diastolic, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure Quintiles in Men and Women.

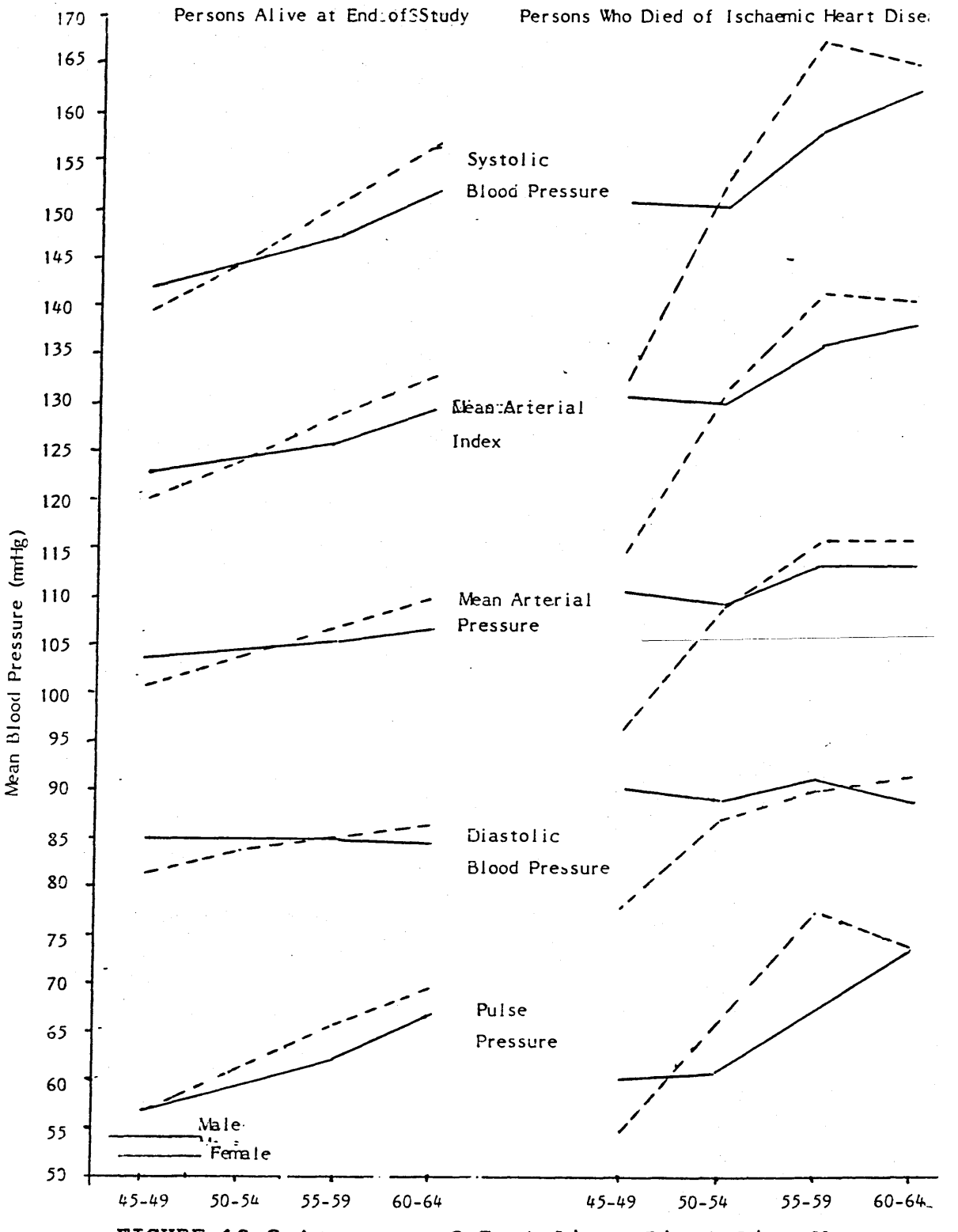


FIGURE 10.3. Average of Systolic, Diastolic, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure in Men and Women.

TABLE 10.1. Systolic and Diastolic Blood Pressure, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure and Standard Normal Deviate by Age Group, for Men Who Were Still Alive and Who Died of Ischaemic Heart Disease After 10-14 Years of Follow-up.

	Died of Ischaemic Heart Disease					Alive at End of Study				
	45-49	50-54	55-59	60-64	All Ages	45-49	50-54	55-59	60-64	All Ages
No. of Cases	34	95	113	130	372	1084	1063	904	748	3799
Systolic Blood Pressure										
Mean	150.8*	150.3*	158.5***	162.2***	157.0***	142.0	144.8	147.1	151.9	145.9
SD	21.4	19.8	21.8	21.8	24.0	19.9	21.2	21.8	22.5	21.5
SND	0.43	0.22	0.45	0.35	0.43	-0.01	-0.03	-0.08	-0.09	-0.07
SD	1.06	0.92	1.01	1.17	1.07	0.99	0.98	1.01	0.95	0.96
Diastolic Blood Pressure										
Mean	90.6*	89.3**	91.3***	88.9***	89.9***	85.2	85.0	84.9	84.6	84.9
SD	12.3	12.3	13.0	13.7	13.0	12.8	12.2	12.9	13.3	12.8
SND	0.41	0.29	0.42	0.26	0.34	-0.005	-0.05	-0.06	-0.05	-0.04
SD	0.95	0.98	0.99	1.02	1.00	0.99	0.97	0.98	0.98	0.98
Mean Arterial Pressure										
Mean	110.7*	109.6**	113.7***	113.3***	112.3***	104.1	104.9	105.6	107.0	105.3
SD	14.1	13.3	15.3	16.7	15.0	14.1	13.8	14.6	14.8	14.3
SND	0.45	0.29	0.47	0.34	0.42	-0.01	-0.04	-0.07	-0.07	-0.05
SD	0.99	0.94	0.95	1.09	1.02	0.99	0.97	0.97	0.97	0.97
Mean Arterial Index										
Mean	130.8**	130.0**	136.1***	137.8***	134.6***	123.1	124.9	126.4	129.5	125.6
SD	17.3	16.0	17.5	21.8	19.0	16.6	17.1	17.8	18.1	17.5
SND	0.45	0.26	0.46	0.35	0.43	-0.01	-0.04	-0.08	-0.08	-0.06
SD	1.03	0.92	0.96	1.14	1.05	0.99	0.98	0.97	0.95	0.96
Pulse Pressure										
Mean	60.2	61.0	67.2**	73.4**	67.1***	56.7	59.8	62.2	67.3	61.0
SD	15.8	15.8	17.3	21.7	19.2	14.1	16.3	16.1	17.4	16.3
SND	0.24	0.07	0.24	0.25	0.30	-0.00	-0.00	-0.06	-0.07	-0.06
SD	1.15	0.97	1.03	1.19	1.13	0.99	0.99	0.96	0.95	0.96

*P<0.05, **P<0.01, ***P<0.001 (Comparing "deceased" with "survive")
Missing=1
Abbreviations: SD=standard deviation, SND=standard normal deviate.

TABLE 10.2. Systolic and Diastolic Blood Pressure, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure and Standard Normal Deviate by Age Group, for Women Who Were Still Alive and Who Died of Ischaemic Heart Disease, After 10-14 Years of Follow-up.

	Died of Ischaemic Heart Disease					Alive at End of Study				
	45-49	50-54	55-59	60-64	All Ages	45-49	50-54	55-59	60-64	All Ages
No. of Cases	11	31	58	81	181	1303	1420	1263	1140	5126
Systolic Blood Pressure										
Mean	132.6	153.2*	167.4***	165.1**	161.8***	139.3	144.9	151.0	157.0	147.7
SD	17.0	24.0	30.3	25.5	27.5	21.3	22.9	25.0	24.7	24.3
SND	-0.32	0.36	0.59	0.29	0.53	-0.005	0.002	-0.05	-0.04	-0.04
SD	0.33	1.05	1.18	1.01	1.11	1.00	1.00	0.97	0.98	0.98
Diastolic Blood Pressure										
Mean	78.2*	87.1	89.9**	91.6***	89.5***	81.7	83.6	85.1	86.5	84.1
SD	8.1	16.4	16.6	12.5	14.5	12.3	12.5	13.2	13.2	13.0
SND	-0.28	0.27	0.33	0.33	0.38	0.006	-0.005	-0.21	-0.03	-0.02
SD	0.66	1.30	1.18	0.90	1.17	1.00	1.00	0.97	0.97	0.98
Mean Arterial Pressure										
Mean	96.3*	109.1	115.8***	116.1***	113.6***	100.9	104.1	107.1	110.0	105.3
SD	5.0	18.0	19.1	14.9	17.2	14.0	14.6	15.7	15.7	15.4
SND	-0.33	0.34	0.50	0.34	0.50	-0.00	-0.00	-0.04	-0.04	-0.03
SD	0.36	1.22	1.19	0.93	1.10	1.00	0.99	0.98	0.98	0.98
Mean Arterial Index										
Mean	114.5**	131.2*	141.6***	140.6**	137.7***	120.1	124.5	129.0	133.5	126.5
SD	4.4	20.7	24.2	19.6	21.9	17.3	18.3	19.9	19.2	19.4
SND	-0.33	0.36	0.56	0.31	0.53	-0.00	0.00	-0.05	-0.04	-0.04
SD	0.26	1.13	1.18	0.98	1.10	1.00	1.00	0.97	0.98	0.98
Pulse Pressure										
Mean	54.4	66.1	77.5***	73.5	72.4***	57.6	61.3	65.8	70.4	63.5
SD	12.5	14.4	22.6	21.1	20.9	15.7	17.1	18.7	19.0	18.2
SND	-0.21	0.29	0.55	0.13	0.44	-0.00	-0.01	-0.05	-0.02	-0.04
SD	0.79	0.85	1.16	1.07	1.12	0.99	1.01	0.96	0.96	0.97

*P<0.05, **P<0.01, ***P<0.001 (Comparing "deceased" with "survive")
Missing=1
Abbreviations: SD=standard deviation, SND=standard normal deviate.

TABLE 10.3. Mean (SD) Standard Normal Deviates Adjusted for Age for Systolic and Diastolic Pressure, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure and Their Difference with Diastolic Pressure by 10-14 Year Mortality Outcome in Males and females.

	Persons Who Died of IHD		Alive at the End of Study	
	Male	Female	Male	Female
No. of Cases	372	181	3799	5126
SBP	0.43(1.07)***	0.53(1.11)***	-0.07(0.96)	-0.04(0.98)
DBP	0.34(1.00)***	0.38(1.17)***	-0.04(0.98)	-0.02(0.98)
MAP	0.42(1.02)***	0.50(1.10)***	-0.05(0.97)	-0.03(0.98)
MAI	0.43(1.05)***	0.53(1.10)***	-0.06(0.96)	-0.04(0.98)
PP	0.30(1.13)***	0.44(1.12)***	-0.06(0.96)	-0.04(0.97)
SBP-DBP	0.09(0.92)	0.15(0.91)*	-0.03(0.80)*	-0.02(0.79)
MAP-DBP	0.08(0.44)***	0.11(0.73)***	-0.01(0.64)*	-0.01(0.39)*
MAI-DBP	0.09(0.74)*	0.15(0.73)**	-0.01(0.38)*	-0.02(0.64)
PP-DBP	-0.03(1.45)	0.05(1.42)	-0.02(1.31)	-0.02(1.25)

Two sample T-test value for persons deceased compared to persons surviving at the end of study and paired T-test to compared the difference between mean of each component of blood pressure and diastolic pressure from zero: *P<0.05, **P<0.01, ***P<0.001.

Abbreviations, SBP=systolic blood pressure, DBP=diastolic blood pressure, MAP=mean arterial pressure, MAI=mean arterial index, PP=pulse pressure.

TABLE 10.4. Ischaemic Heart Disease Mortality in Upper Age, Gender Specific and Adjusted Quintile of Systolic and Diastolic Blood Pressure, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure.

	Age Group				All Ages	Age-adjusted Rate@
	45-49	50-54	55-59	60-64		
Male						
Diastolic Blood Pressure						
No. of Deaths	8	24	43	38	113	113
Death Rate	3.2	10.3	19.0	19.7	12.5	12.8
Systolic Blood pressure						
No. of Deaths	6	17	37	48	108	108
Death Rate	4.4	9.8	19.4	22.4	11.4	13.7
Rate Ratio SBP/DPB	1.40	0.96	1.02	1.14	0.91	1.07
Mean Arterial Pressure						
No. of Deaths	5	23	46	47	121	121
Death Rate	2.5	10.8	21.2	22.7	14.5	14.1
Rate Ratio MAP/DBP	0.78	1.07	1.11	1.10	1.16	1.08
Mean Arterial Index						
No. of Deaths	6	20	38	50	114	114
Death Rate	3.9	10.3	19.3	23.2	15.0	13.9
Rate Ratio MAI/DBP	1.23	1.02	1.02	1.13	1.20	1.07
Pulse pressure						
No. of Deaths	5	11	33	50	99	99
Death Rate	4.9	6.6	17.7	21.1	14.3	12.3
Rate Ratio PP/DBP	1.54	0.65	0.93	1.03	1.15	0.95
Female						
Diastolic Blood Pressure						
No. of Deaths	0	10	22	28	60	60
Death Rate	0.0	4.0	7.1	8.3	5.5	4.7
Systolic Blood pressure						
No. of Deaths	0	9	28	36	73	73
Death Rate	0.0	3.4	8.0	8.1	6.0	4.8
Rate Ratio SBP/DPB	1.00	0.85	1.13	0.98	1.09	1.01
Mean Arterial Pressure						
No. of Deaths	0	10	27	36	73	73
Death Rate	0.0	3.7	8.1	8.9	6.2	5.1
Rate Ratio MAP/DBP	1.00	1.07	1.20	1.09	1.19	1.3
Mean Arterial Index						
No. of Deaths	0	10	28	37	75	75
Death Rate	0.0	3.7	7.9	8.8	6.2	5.0
Rate Ratio MAI/DBP	1.00	1.06	1.17	1.07	1.19	1.11
Pulse pressure						
No. of Deaths	1	7	23	30	61	61
Death Rate	0.6	2.6	6.5	6.8	4.9	4.0
Rate Ratio PP/DBP	-	0.74	0.95	0.82	0.94	0.89

@Death rate per 1,000 person year of observation age-adjusted to 1981 Scottish population.

Table 10.5. Coefficients of Correlation Between Blood Pressure Measures, in Men and Women.

	Diastolic BP	Mean Arterial Pressure	Mean Arterial Index	Pulse Pressure
		Male		
Systolic BP	0.657	0.896	0.983	0.816
Diastolic BP		0.924	0.782	0.101
Mean Art. pres.			0.961	0.553
Mean Art. Index				0.699
		Female		
Systolic BP	0.672	0.908	0.986	0.851
Diastolic BP		0.920	0.785	0.182
Mean Art. Pres.			0.965	0.553
Mean Art. Index				0.752

TABLE 10.6. Univariate Multiple Logistic Coefficients@ and Odds Ratio of Ischaemic Heart Disease Mortality on Various Components of Blood Pressure in 10-14 Years Follow-up by Gender.

Blood Pressure Component	Male			Female		
	Logistic Coefficient@	Odds Ratio	Z-Test	Logistic Coefficient	Odds Ratio	Z-Test
Systolic BP	0.020	1.62	8.9***	0.021	1.67	7.4***
Diastolic BP	0.027	1.42	6.7***	0.028	1.44	5.1***
Pulse Pressure (SBP-DBP)	0.021	1.50	6.7***	0.024	1.55	6.3***
Mean Arterial Pressure (DBP+PP/3)	0.030	1.56	8.4***	0.031	1.62	6.8***
Mean Arterial Index (2*SBP+DBP)/3	0.026	1.64	8.9***	0.026	1.61	7.3***

@Walker-Duncan evaluation of logistic parameters (139).
*P<0.5, **P<0.01, ***P<0.001
£The odds ratio for a change in the risk factor by an amount equal to its standard deviation.

TABLE 10.7. Multiple Logistic Coefficients and Standardised Odds Ratio of Systolic and Diastolic Blood Pressure and Five Other Risk Factors for 10-14 Years Mortality from IHD by Gender and Single Systolic or Diastolic and Both Systolic and Diastolic Blood Pressure.

	Male			Female		
Variables	Logistic Coefficient	Odds Ratio@	Z-Test	Logistic Coefficient	Odds Ratio@	Z-Test
Single Systolic Blood Pressure						
Age	0.088	1.62	8.16***	0.116	1.89	6.77***
Systolic BP	0.017	1.45	7.22***	0.014	1.41	4.80***
Serum Choles.	0.004	1.16	2.84**	0.005	1.23	2.70**
Blood Glucose	0.003	1.08	1.29	0.011	1.28	5.92***
Cig. Smoking£	0.210	1.52	3.64***	0.323	1.91	3.91***
BMI	0.029	1.10	1.65	0.002	1.01	0.12
Single Diastolic Blood Pressure						
Age	0.103	1.76	9.61***	0.126	2.00	7.52***
Diastolic BP	0.030	1.47	7.09***	0.022	1.33	3.95***
Serum Choles.	0.004	1.16	2.90**	0.005	1.23	2.66**
Blood Glucose	0.004	1.11	2.16*	0.011	1.28	6.32***
Cig. Smoking£	0.257	1.67	4.42***	0.334	1.95	4.05***
BMI	0.016	1.05	0.90	0.002	1.01	0.13
Single Mean Arterial Pressure						
Age	0.096	1.69	8.92***	0.120	1.93	7.06***
MAP	0.029	1.52	7.84***	0.023	1.43	4.79***
Serum Choles.	0.004	1.16	2.79**	0.005	1.23	2.64**
Blood Glucose	0.003	1.08	1.75	0.011	1.28	6.07***
Cig. Smoking£	0.239	1.61	4.12***	0.335	1.95	4.05***
BMI	0.016	1.05	0.88	0.003	1.05	0.16
Single Mean Arterial Index						
Age	0.091	1.64	8.41***	0.117	1.90	6.84***
MAI	0.023	1.50	7.66***	0.019	1.45	4.91***
Serum Choles.	0.004	1.16	2.81**	0.005	1.23	2.67**
Blood Glucose	0.003	1.08	1.51	0.011	1.28	5.95***
Cig. Smoking£	0.223	1.56	3.85***	0.329	1.93	3.98***
BMI	0.021	1.07	1.22	0.001	1.00	0.05

TABLE 10.7.Continued

Variables	Male			Female		
	Logistic Coefficient	Odds Ratio@	Z-Test	Logistic Coefficient	Odds Ratio@	Z-Test
Single Pulse Pressure						
Age	0.091	1.64	8.31***	0.119	1.92	6.97***
Pulse Pressure	0.013	1.24	4.02***	0.014	1.29	3.52***
Serum Choles.	0.004	1.16	2.71**	0.005	1.23	2.82**
Blood Glucose	0.003	1.08	1.41	0.011	1.28	6.05***
Cig. Smoking£	0.212	1.53	3.62***	0.298	1.81	3.6***
BMI	0.048	1.17	2.81**	0.016	1.07	0.95
Both Systolic and Diastolic Blood Pressure						
Age	0.095	1.69	8.57***	0.116	1.89	6.77***
Systolic BP	0.011	1.27	3.25**	0.014	1.41	4.80***
Diastolic BP	0.017	1.24	3.03**	0.008	1.11	1.05
Serum Choles.	0.004	1.16	2.79**	0.005	1.23	2.70**
Blood Glucose	0.003	1.08	1.72	0.011	1.28	5.92***
Cig. Smoking£	0.239	1.16	4.05***	0.323	1.91	3.91
BMI	0.016	1.05	0.90	0.002	1.01	0.09

@The approximate relative risk (odds ratio) for a change in the risk factor by an amount equal to its standard deviation.
£The odds ratio calculated for smokers and non-smokers.
*P<0.05, **P<0.01, ***P<0.001
168 deaths in 5321 female and 350 death in 4171 males.

TABLE 10.8. Multiple Logistic Coefficients and Standardised Odds Ratio of Systolic and Diastolic Blood Pressure Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure for 10-14 Years Mortality from IHD by Gender and Single Systolic or Diastolic or Mean Arterial Pressure or Mean Arterial Index, or Pulse pressure and Both Systolic and Diastolic Blood Pressure.

	Male			Female		
Variables	Logistic Coefficient	Odds Ratio@	Z-Test	Logistic Coefficient	Odds Ratio@	Z-Test
Single component of Blood Pressure						
Systolic BP	0.017	1.45	7.22***	0.014	1.40	4.80***
Diastolic BP	0.030	1.47	7.09***	0.022	1.33	3.95***
MAP	0.029	1.52	7.84***	0.023	1.43	4.8***
MAI	0.022	1.48	7.6***	0.019	1.45	4.9***
PP	0.013	1.24	4.0***	0.014	1.29	3.5***
Both Systolic and Diastolic Blood Pressure						
Systolic BP	0.011	1.27	3.25**	0.014	1.22	4.80***
Diastolic BP	0.017	1.24	3.03**	0.008	1.11	1.05

@The approximate relative risk (odds ratio) for a change in the risk factor by an amount equal to its standard deviation.
£The odds ratio calculated for smokers and non-smokers.
*P<0.05, **P<0.01, ***P<0.001
168 deaths in 5321 female and 350 death in 4171 males.
Abbreviations: BP=blood pressure, MAP=mean arterial pressure, MAI=mean arterial index, PP=pulse pressure.

TABLE 10.9. Summary of Standard Normal Deviate Separating Survivors from Men Who Died of IHD and Standardised Odds Ratio and Rate Ratio of Age-Adjusted and Crude Death Rate in Upper Quintile of Systolic and Diastolic Pressure in Present Study and Whitehall Study.

Age Group	Renfrew and Paisley Study		Whitehall Study	
	Systolic	Diastolic	Systolic	Diastolic
	Standard normal deviate			
40-44	-	-	0.01	0.20
45-49	0.43	0.41	0.54	0.50
50-54	0.22	0.29	0.34	0.28
55-59	0.45	0.42	0.47	0.44
60-64	0.35	0.26	0.42	0.24
All Ages	0.43	0.34	0.42	0.35
Standardised Odds Ratio for Single Systolic and Diastolic Pressure				
	1.50	1.48	1.37	1.31
Standardised Odds Ratio for Both Systolic and Diastolic Pressure				
	1.27	1.24	1.29	1.09
Systolic and Diastolic Rate Ratio of Age-Adjusted and Crude Mortality In Upper Quintile				
Adjusted	1.06		1.05	
Crude	1.22		1.15	

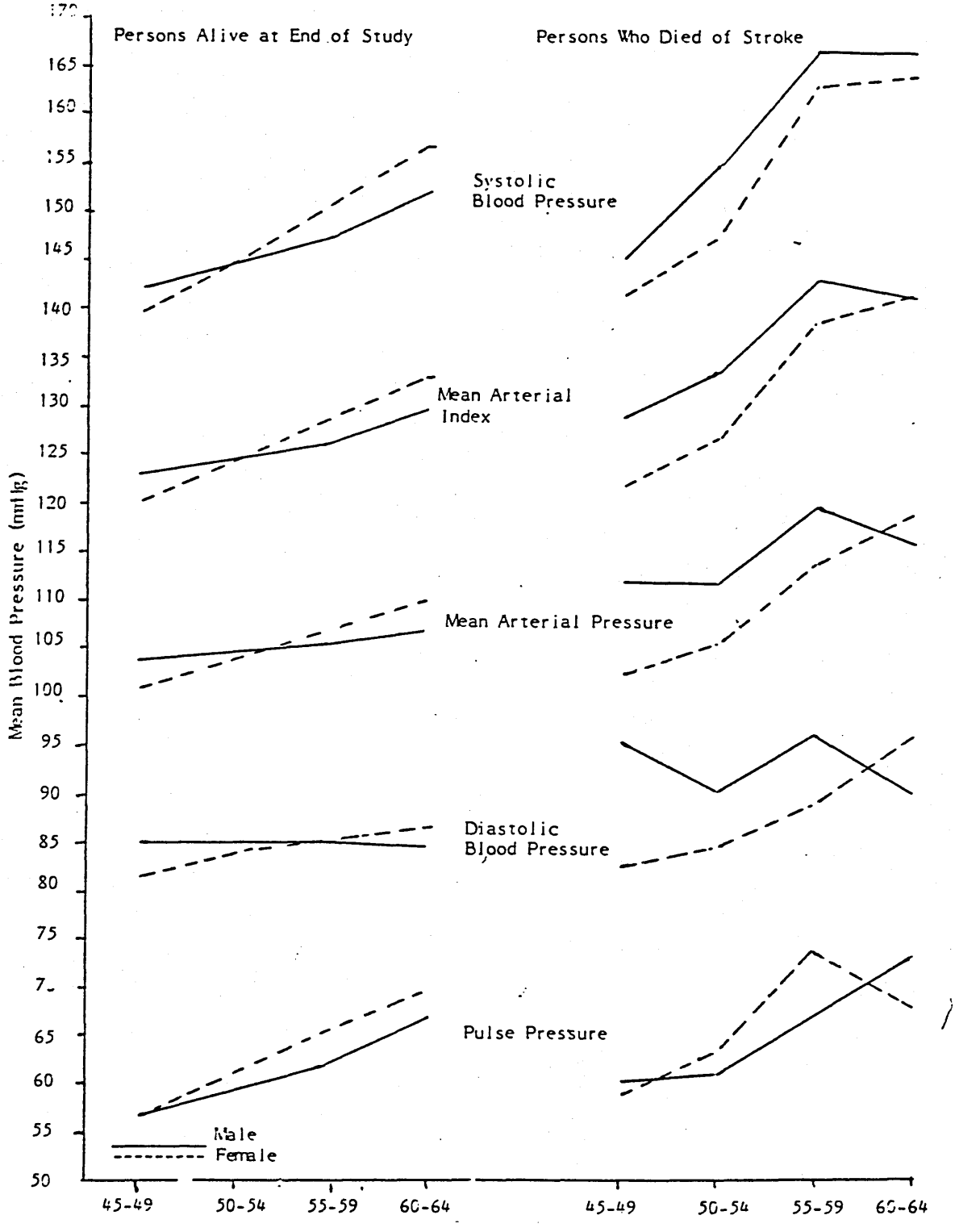


FIGURE 11.1. Average of Systolic, Diastolic, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure at Initial Examination by Gender.

TABLE 11.1. Systolic and Diastolic Blood Pressure, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure and Standard Normal Deviate by Age Group, for Men Who Survived and Who Died of Stroke After 10-14 Years of Follow-up.

Age (Yr)	Alive at End of Study			Died of stroke		
	NO. of Cases	Mean (SD)	Standardized Normal Devi. (SD)	No. of Cases	Mean (SD)	Standardized Normal Devi. (SD)
Systolic Blood Pressure						
45-49	1084	142.0(19.9)	-0.01(0.99)	3	145.7(40.1)	0.17(1.99)
50-54	1063	144.8(21.2)	-0.03(0.98)	15	154.9(25.8)	0.44(1.20)
55-59	904	147.1(21.8)	-0.08(1.01)	33	166.9(28.5)***	0.82(1.32)***
60-64	748	151.9(22.5	-0.09(0.95)	29	166.3(29.4)*	0.52(1.24)*
Diastolic Blood Pressure						
45-49	1084	85.2(19.9)	-0.01(0.99)	3	95.3(18.5)	0.78(1.43)
50-54	1063	85.0(12.2)	-0.05(0.97)	15	90.4(15.5)	0.38(1.23)
55-59	904	84.9(12.9)	-0.06(0.98)	33	96.0(17.5)***	0.78(1.33)***
60-64	748	84.6(13.3)	-0.05(0.98)	29	90.0(16.4)*	0.35(1.22)*
Mean Arterial Pressure						
45-49	1084	104.1(14.1)	-0.01(0.99)	3	112.1(25.4)	0.55(1.79)
50-54	1063	104.9(13.8)	-0.04(0.97)	15	111.9(18.5)	0.45(1.30)
55-59	904	105.6(14.6)	-0.07(0.97)	33	119.0(20.0)***	0.85(1.33)***
60-64	748	107.0(14.8)	-0.07(0.97)	29	115.4(19.5)*	0.47(1.28)*
Mean Arterial Index						
45-49	1084	123.1(16.6)	-0.01(0.99)	3	128.9(32.7)	0.34(1.95)
50-54	1063	124.9(17.1)	-0.04(0.98)	15	133.4(22.0)	0.45(1.27)
55-59	904	126.4(17.8)	-0.08(0.97)	33	143.0(23.8)***	0.83(1.30)***
60-64	748	129.5(18.1)	-0.08(0.95)	29	140.9(24.1)***	0.51(1.27)***
Pulse Pressure						
45-49	1084	56.7(14.1)	-0.00(0.99)	3	50.3(23.0)	-0.45(1.62)
50-54	1063	59.8(16.3)	-0.00(0.99)	15	64.5(13.5)	0.28(1.22)
55-59	904	62.2(16.1)	-0.06(0.96)	33	70.5(18.7)*	0.43(1.11)*
60-64	748	67.3(17.4)	-0.07(0.95)	29	76.2(19.7)*	0.41(1.08)*

*P<0.05, **P<0.01, ***P<0.001 (Comparing "deceased" with "survive").

TABLE 11.2. Systolic and Diastolic Blood Pressure, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure and Standard Normal Deviate by Age Group, for Women Who Survived and Who Died of Stroke After 10-14 Years of Follow-up.

Age (Yr)	Alive at End of Study			Died of stroke		
	NO. of Cases	Mean (SD)	Standardized Normal Devi. (SD)	No. of Cases	Mean (SD)	Standardized Normal Devi. (SD)
Systolic Blood Pressure						
45-49	1303	139.3(21.3)	0.00(1.00)	7	141.3(21.1)	0.09(1.01)
50-54	1420	144.9(22.9)	0.00(1.00)	10	147.8(25.2)	0.13(1.11)
55-59	1263	151.0(25.0)	-0.05(0.97)	18	163.0(25.4)*	0.42(0.99)*
60-64	1140	157.0(24.7)	-0.04(0.98)	45	163.7(25.1)	0.23(1.00)
Diastolic Blood Pressure						
45-49	1303	81.7(12.3)	0.01(1.00)	7	82.6(16.2)	0.08(1.31)
50-54	1420	83.6(12.5)	0.00(1.00)	10	84.2(11.6)	0.04(0.92)
55-59	1263	85.1(13.2)	-0.02(0.97)	18	88.9(14.3)	0.26(1.05)
60-64	1140	86.5(13.2)	-0.03(0.97)	45	95.9(15.5)***	0.64(1.11)***
Mean Arterial Pressure						
45-49	1303	100.9(14.0)	0.00(1.00)	7	102.1(16.5)	0.09(1.65)
50-54	1420	104.1(14.6)	0.00(0.99)	10	105.4(15.2)	0.09(1.03)
55-59	1263	107.1(15.7)	-0.04(0.98)	18	113.6(16.6)	0.37(1.03)
60-64	1140	110.0(15.7)	-0.04(0.98)	45	118.5(16.9)***	0.49(1.06)***
Mean Arterial Index						
45-49	1303	120.1(17.3)	0.00(1.00)	7	121.7(18.3)	0.09(1.06)
50-54	1420	124.5(18.3)	0.00(1.00)	10	126.6(19.9)	0.11(1.09)
55-59	1263	129.0(19.9)	-0.05(0.97)	18	138.3(20.0)	0.41(1.02)
60-64	1140	133.5(19.2)	-0.04(0.98)	45	141.1(20.4)*	0.34(1.01)*
Pulse Pressure						
45-49	1303	57.6(15.7)	0.00(0.99)	7	58.7(15.2)	0.58(1.47)
50-54	1420	61.3(17.1)	-0.01(1.01)	10	63.6(17.9)	0.14(1.06)
55-59	1263	65.8(18.7)	-0.05(0.96)	18	74.0(20.1)	0.37(1.03)
60-64	1140	70.4(19.0)	-0.02(0.96)	45	67.8(19.6)	-0.16(0.99)

*P<0.05, **P<0.01, ***P<0.001 (Comparing "deceased" with "survive")

TABLE 11.3. Mean (SD) Standard Normal Deviates Adjusted£ for Age for Systolic (SBP) and Diastolic Pressure (DBP), Mean Arterial Pressure (MAP), Mean Arterial Index (MAI) and Pulse Pressure (PP) and Their Difference with DBP by 10-14 Year Mortality Outcome, in Men and Women.

Blood Pressure Components	Male		Female	
	Alive at the End of Study	Died of Stroke	Alive at the End of Study	Died of Stroke
No. of Cases	3799	80	5126	80
SBP	-0.05(0.96)	0.49(1.28)***	-0.02(0.98)	0.22(1.00)***
DBP	-0.04(0.98)	0.57(1.29)***	-0.01(0.98)	0.25(1.17)***
MAP	-0.05(0.97)	0.58(1.33)***	-0.02(0.98)	0.26(1.11)***
MAI	-0.05(0.96)	0.53(1.31)***	-0.02(0.98)	0.24(1.06)***
PP	-0.03(0.96)	0.17(1.12)**	-0.02(0.97	0.23(1.00)*
SBP-DBP	-0.01(0.80)	-0.08(0.86)	-0.01(0.79)	-0.03(0.91)
MAP-DBP	-0.01(0.38)	0.01(0.41)	-0.01(0.39)	0.01(0.43)
MAI-DBP	-0.01(0.64)	-0.04(0.69)	-0.01(0.64)	-0.01(0.73)
PP-DBP	0.01(1.31)	-0.40(1.43)**	-0.01(1.25)	-0.02(1.49)

Two sample t-test value for persons died compared to persons alive at the end of study and paired t-test to compare the difference between mean of each component of blood pressure and diastolic pressure from zero: *P<0.05, **P<0.01, ***P<0.001.

£Age-adjusted mean standard normal deviate by averaging five year age-group.

TABLE 11.4. Cerebrovascular Disease Mortality in Upper Age, Gender Specific and Adjusted Quintile of Systolic and Diastolic Blood Pressure, Mean Arterial Pressure, Mean Arterial Index and Pulse Pressure.

	Age Group				All Ages	Age-Adjusted Rate
	45-49	50-54	55-59	60-64		
Male						
Diastolic Blood Pressure						
No. of Deaths	2	3	18	8	31	31
Death Rate	0.8	1.3	8.6	4.5	3.6	3.8
Systolic Blood pressure						
No. of Deaths	1	4	18	13	35	35
Death Rate	0.8	2.4	10.0	6.1	5.2	4.8
Rate Ratio SBP/DPB	0.94	1.80	1.16	1.34	1.43	1.26
Mean Arterial Pressure						
No. of Deaths	2	4	17	10	33	33
Death Rate	1.0	2.0	8.6	5.4	4.2	4.2
Rate Ratio MAP/DBP	1.25	1.47	0.99	1.19	1.16	1.10
Mean Arterial Index						
No. of Deaths	1	4	17	12	34	34
Death Rate	0.7	2.2	9.3	6.1	4.8	4.5
Rate Ratio MAI/DBP	0.83	1.61	1.07	1.35	1.32	1.18
Pulse pressure						
No. of Deaths	0	2	14	12	28	28
Death Rate	0.0	1.2	8.1	5.6	4.3	3.7
Rate Ratio PP/DBP	0	0.92	0.94	1.23	1.19	0.97
Female						
Diastolic Blood Pressure						
No. of Deaths	1	2	5	24	30	30
Death Rate	0.5	0.8	1.7	6.7	2.8	2.3
Systolic Blood pressure						
No. of Deaths	0	2	6	19	27	27
Death Rate	0.0	0.7	1.8	4.5	2.3	1.7
Rate Ratio SBP/DPB	0.0	0.93	1.06	0.67	0.81	0.73
Mean Arterial Pressure						
No. of Deaths	1	2	8	20	31	31
Death Rate	0.6	0.7	2.5	5.2	2.7	2.2
Rate Ratio MAP/DBP	1.13	0.93	1.49	0.78	0.97	0.95
Mean Arterial Index						
No. of Deaths	0	2	8	19	30	30
Death Rate	0.0	0.7	2.3	4.7	2.6	1.9
Rate Ratio MAI/DBP	0	0.92	1.40	0.70	0.91	0.82
Pulse pressure						
No. of Deaths	1	3	7	15	26	26
Death Rate	0.6	1.1	2.0	3.5	2.1	1.7
Rate Ratio PP/DBP	1.13	1.35	1.20	0.52	0.76	0.76

Death rate per 1,000 person years of observation age-adjusted to 1981 Scottish population by four five year age-groups.

TABLE 11.5. Univariate Logistic Regression Coefficients@ and Odds Ratio£ of Cerebrovascular Disease Mortality on Various Components of Blood Pressure in 10-14 Years Follow-up by Gender,

Blood Pressure Component	Male			Female		
	Logistic Coefficient	Odds Ratio	Z-Test	Logistic Coefficient	Odds Ratio	Z-Test
Systolic BP	0.030	1.93	6.9***	0.019	1.59	4.7***
Diastolic BP	0.042	1.71	5.7***	0.039	1.67	5.1***
Mean Arterial Pressure (DBP+PP/3)	0.043	1.85	6.8***	0.034	1.69	5.3***
Mean Arterial Index (2*SBP+DBP/3)	0.037	1.92	7.0***	0.025	1.63	5.0***
Pulse Pressure (SBP-DBP)	0.030	1.64	4.9***	0.015	1.32	2.6**

@Walker-Duncan evaluation of logistic parameters (139).
£The approximate relative risk (standardized odds ratio) for a change in the risk factor by an amount equal to its standard deviation.
*P<0.5, **P<0.01, ***P<0.001

TABLE 11.6. Multiple Logistic Coefficients and Standardised Odds Ratio of Systolic (SBP) and Diastolic Blood Pressure (DBP) Mean Arterial Pressure (MAP), Mean Arterial Index (MAI) and Pulse Pressure (PP) for 10-14 Years Mortality from Stroke by Gender and Single SBP, DBP, MAP, MAI or PP and Both SBP and DBP.

Blood Pressure Variables	Male			Female		
	Logistic Coefficient	Odds Ratio@	Z-Test	Logistic Coefficient	Odds Ratio@	Z-Test
Single component of Blood Pressure						
SBP	0.027	1.81	5.91***	0.015	1.44	3.40***
DBP	0.045	1.78	6.03***	0.044	1.78	5.25***
MAP	0.043	1.86	6.50***	0.035	1.72	4.90***
MAI	0.035	1.85	6.30***	0.023	1.57	4.12***
PP	0.020	1.39	3.20**	0.005	1.10	0.77
Both Systolic and Diastolic Blood Pressure						
SBP	0.015	1.39	2.42*	0.001	1.02	0.24
DBP	0.027	1.41	2.58*	0.044	1.78	5.25***

@The approximate relative risk (odds ratio) for a change in the risk factor by an amount equal to its standard deviation.
*P<0.05, **P<0.01, ***P<0.001
80 deaths in 5,232 female and 79 death in 3,900 males.

TABLE 12.1. Number of Linked cases

	Number	Percent
Total linked	981	100.0
Matched by Computer	870	88.7
Matched by Microfiche	67	6.8
Not Matched	44	4.5

TABLE 12.2. Distribution of Individuals Identified and not Identified by Postal Contact.

	Number	Percent
Total no. matched with CHI	937	100.0
No. identified	745	79.5
No. not identified	192	20.5
Not traced	65	33.8
No reply to questionnaire	95	49.5
Transferred	32	16.7

TABLE 12.3. Distribution of Response Rate by Case and Control.

	Total Issue	Response							
		Original		First Reminder		Second Reminder		Total	
		No.	(%)	NO.	(%)	No.	(%)	No.	(%)
Case	238	149	(62.6)	25	(28.0)	10	(15.6)	184	(77.3)
Control 1	443	274	(61.8)	59	(34.9)	21	(19.1)	354	(79.9)
Control 2	256	166	(64.8)	34	(37.8)	7	(8.4)	207	(80.8)
Total	937	589	(62.9)	118	(33.9)	38	(16.5)	745	(79.5)

TABLE 13.1. Follow-up Data and Life-Table Projections of Progress to Diabetes Among 224 Men and Women with Casual Post-Prandial Blood Glucose Above 126 mg/dl.

	Male				Female			
X	O z	W n z	D n z	I z	O z	W n z	D n z	I z
0	114	0	0	0	108	0	0	0
1	114	0	0	0	108	0	2	1.8
2	114	0	0	0	106	0	0	1.8
3	114	0	0	0	106	0	0	1.8
4	114	0	3	2.6	106	0	1	2.8
5	111	0	3	5.3	105	0	1	3.7
6	108	0	2	7.0	104	0	2	5.6
7	106	0	0	7.0	102	0	1	6.5
8	106	0	2	8.8	101	0	1	7.4
9	104	0	4	12.3	100	0	1	8.3
10	100	0	0	12.3	99	0	0	8.3
11	100	0	1	13.6	99	0	0	8.3
12	99	59	0	13.6	99	60	3	12.5
13	40	39	1	13.6	30	30	0	12.5

X=Year after diagnosis of asymptomatic hyperglycaemia; O=Number observed X or more year after diagnosis; W=Number last observed without worsening between X and next stated X year; D=number worsening between this X and next stated X year I=estimated cummulative percent incidence of worsening at X year.

$$I = 1 - \frac{{}_{n}D_{z}}{{}_{z-1/2}O_{W}}$$

TABLE 13.2. Twelve to Fourteen Years Follow-up Related to Initial Casual Post-Prandial Blood Glucose Level by Age and Gender.

Age Group	Male								Female							
	Initial Blood Glucose								Initial Blood Glucose							
	≥126		=90		<70		Total		≥126		=90		<70		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
45-49	4	13.3	2	6.0	-	-	6	4.9	1	4.3	-	-	-	-	1	0.8
50-54	6	19.3	-	-	-	-	6	5.3	1	4.3	-	-	-	-	1	0.8
55-59	2	8.3	1	4.3	1	2.2	4	4.3	8	21.6	1	3.2	-	-	9	7.0
60-64	4	13.3	-	-	1	3.3	5	6.2	2	7.1	1	2.2	1	2.6	4	3.6
Total	16	13.9	3	3.0	2	1.0	21	5.4	12	11.0	2	1.3	1	0.4	15	3.0

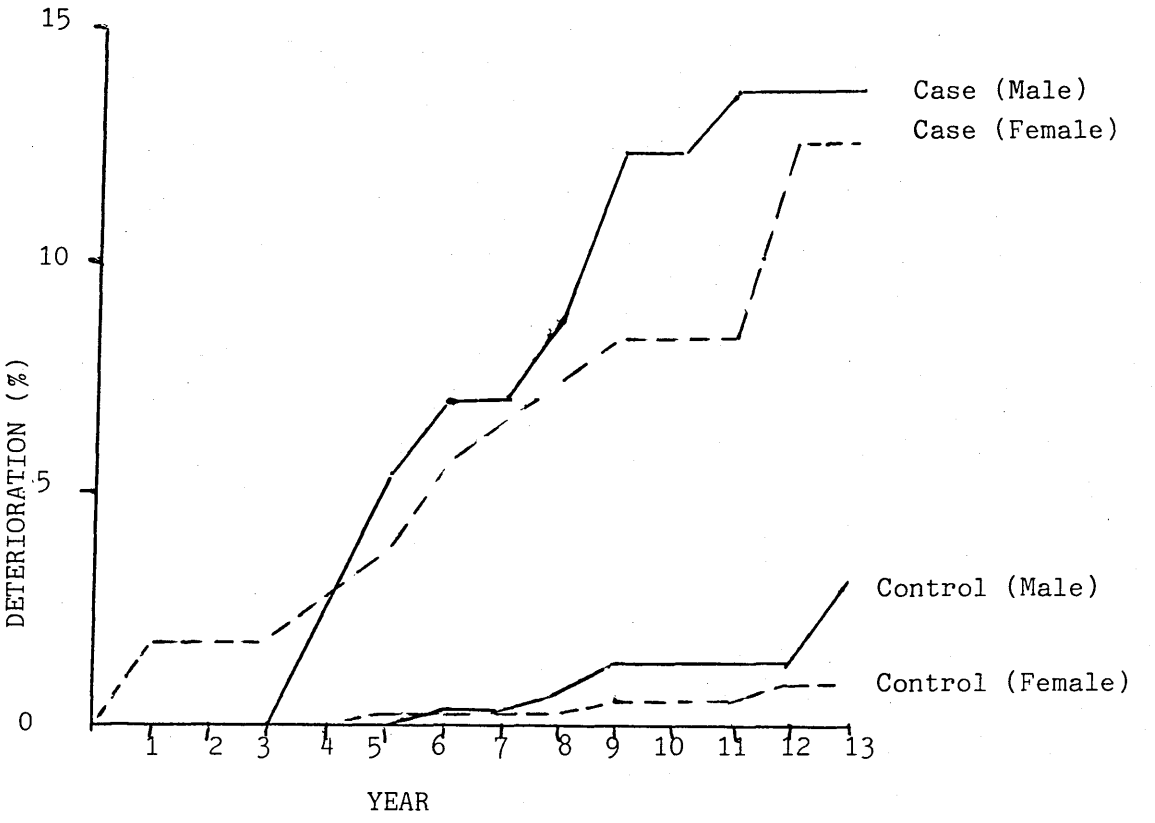


FIGURE 13.1. Projected Rates of Progression to Diabetes by Gender in Case and Control Groups.

TABLE 13.3. Initial Age Distribution by Causal Post-Prandial Blood Glucose level.

Age Group	Male						Female					
	Initial Blood Glucose						Initial Blood Glucose					
	≥126		=90		<70		≥126		=90		<70	
	NO.	%	No.	%	No.	%	No.	%	No.	%	No.	%
45-49	30	26.1	33	33.3	60	30.6	21	19.3	39	25.3	64	27.8
50-54	31	26.9	23	23.2	60	30.6	23	21.1	40	26.0	66	28.7
55-59	24	20.9	23	23.2	46	23.5	37	33.9	31	20.1	61	26.5
60-64	30	26.1	20	20.2	30	15.3	28	25.7	44	28.6	39	16.9
Total	115	100.0	99	100.0	196	100.0	109	100.0	154	100.0	230	100.0
Mean	54.9(5.8)		54.0(6.0)		53.6(5.4)		55.6(5.6)		55.3(5.9)		54.1(5.3)	
Median	54.7		52.9		53.3		55.7		55.0		53.9	

Standard deviation of age is in bracket.

TABLE 13.4. Comparison of Baseline Variables in Those Who Did or Did Not Developed Diabetes (Mean and Standard Error in Each Group).

Variable	Developed Diabetes	Not Developed Diabetes	95% Confidence Interval
		MALE	
Number	22.0	388.0	-
Sugar	174.3(23.0)***	89.6(1.8)	39.5-129.9
Age	54.0(0.3)	54.0(1.3)	-
SBP	154.5(5.2)	144.0(1.0)	-
DBP	91.0(3.0)*	83.0(0.6)	2-14
BMI	27.6(0.8)*	25.6(0.2)	0.4-3.6
Cholest	229.0(7.3)	231.0(1.8)	-
Smoking(%)	31.8	44.8	-
		FEMALE	
Number	16.0	477.0	-
Sugar	175.5(23.5)***	87.4(1.5)	42.0-134.2
Age	57.7(1.0)*	54.7(0.2)	0.9-5.1
SBP	162.6(6.6)*	143.7(1.0)	5.8-32
DBP	89.2(2.6)*	82.1(0.6)	1.9-12.3
BMI	29.0(1.2)**	25.1(0.2)	1.5-6.3
Cholest	252.1(8.1)	252.5(2.3)	-
Smoking(%)	37.5	44.7	-

Significantly different from non-diabetics, *P<0.05, **P<0.01, ***P<0.001.

TABLE 13.5. Bivariate Analysis, Dichotomization of Baseline Variables and 12 to 14 Year Incidence Rate of Deterioration to Diabetes and Risk Factor Status, in Men and Women.

Risk Factor		Male			Female			Gender
		Incidence Rate/1000@		Relative Risk (a/b)	Incidence Rate/1000@		Relative Risk (a/b)	Ratio
(a)Blood	≥126	11.6	(16)	8.92***	9.2	(12)	15.3***	1.3
(b)Glucose	<126	1.3	(5)	-	0.6	(3)	-	2.2
(a)Systolic	≥160	7.7	(8)	2.41*	4.8	(7)	2.82*	1.6
(b)BP	<160	3.2	(13)	-	1.7	(8)	-	1.9
(a)Diastolic	≥95	10.4	(9)	3.71**	3.2	(3)	1.39	3.2
(b)BP	<95	2.8	(12)	-	2.3	(12)	-	1.2
(a)Serum	≥250	4.8	(7)	1.26	1.8	(6)	0.58	2.7
(b)Chol.	<250	3.8	(14)	-	3.1	(9)	-	1.2
(a)BMI	≥27	6.3	(11)	2.10*	6.1	(10)	5.5***	1.0
(b)	<27	3.0	(10)	-	1.1	(5)	-	2.7
(a)Use of	Yes	3.0	(7)	0.60	2.2	(6)	0.84	1.4
(b)Cigarette	No	5.0	(14)	-	2.6	(9)	-	1.9
All		4.1	(21)	-	2.4	(15)	-	1.7

@Incidence rate per 1,000 person year of observation.
Number in brackets refer to number of diabetes.

TABLE 13.6. Comparison of Baseline Variables in Index and Comparison Groups for Males and Females (Mean and Standard Error in Each Group) As Reported at Time of Their Participation In Midspan Survey and Multiple Correlation Coefficients with Blood Sugar.

Variable	Index Group	Comparison Group	95% CI	Regression Coefficient with Blood Glucose
		Male		
Numbers	115	295		
Sugar	153.4 (4.6)***	71.0 (0.8)	72.9-91.2	-
Age	54.9 (0.5)	53.7 (0.3)	-	0.4030
SBP	150.5 (2.2)***	142.3 (1.1)	3.4-13	0.1241*
DBP	83.7 (1.4)	83.3 (0.7)	-	-0.0835
BMI	26.3 (0.3)*	25.5 (0.2)	0.1-1.5	0.1390**
Cholest	231.6 (3.0)	230.6 (2.1)	-	0.0008
Smoking(%)	34.8	47.8*	-	-
		Female		
Numbers	109	384		
Sugar	150.2 (3.6)***	73.3 (0.7)	73.1-80.7	-
Age	55.6 (0.5)	54.6 (0.3)	-	-0.0076
SBP	153.4 (2.5)***	141.8 (1.1)	6.1-16.7	0.3963***
DBP	83.7 (1.2)	82.0 (0.6)	-	-0.2364***
BMI	25.9 (0.4)*	25.0 (0.2)	0.0-1.8	0.1324**
Cholest	254.3 (4.5)	252.0 (2.6)		0.0045
Smoking(%)	39.4	45.8		-

The correlation coefficient calculated based on multiple regression model.
The standard error shown in bracket.
Significantly different from comparisons, *P<0.05, **P<0.01, ***P<0.001.

TABLE 13.7. Bivariate Analysis, Dichotomization of Baseline Variables and 12 to 14 Year Incidence Rates of Deterioration to Diabetes and Risk Factor Status, in Index and Comparison Groups, in Men and Women.

Risk Factor		Index Group		Comparison Group		Index-Comparison Rate Ratio
		Incidence Rate/1000@	RR (a/b)	Incidence Rate/1000@	RR (a/b)	
Male						
(a)Systolic	≥160	14.8 (6)	1.44	3.1 (2)	3.10	4.77
(b)BP	<160	10.3 (10)	-	1.0 (3)	-	10.62
(a)Diastolic	≥95	23.2 (7)	2.76	3.5 (3)	3.72	6.62
(b)BP	<95	8.4 (9)	-	0.9 (2)	-	8.93
(a)Serum	≥250	11.7 (5)	1.01	1.9 (2)	1.72	6.16
(b)Chol.	<250	11.6 (11)	-	1.1 (3)	-	10.54
(a)BMI	≥27	16.6 (9)	1.98	1.7 (2)	1.42	9.76
(b)	<27	8.4 (7)	-	1.2 (3)	-	7.00
(a)Use of	Yes	12.7 (5)	1.29	1.5 (2)	1.36	8.47
(b)Cigarette	No	9.8 (11)	-	1.1 (3)	-	8.91
All		11.6 (16)	-	1.3 (5)	-	8.92
Female						
(a)Systolic	≥160	11.5 (6)	1.49	1.1 (1)	2.20	10.45
(b)BP	<160	7.7 (6)	-	0.5 (2)	-	15.40
(a)Diastolic	≥95	13.2 (3)	1.57	0.0 (0)	-	-
(b)BP	<95	8.4 (9)	-	0.7 (3)	-	11.67
(a)Serum	≥250	5.7 (4)	0.59	0.8 (2)	2.00	7.50
(b)Chol.	<250	9.6 (8)	-	0.4 (1)	-	21.82
(a)BMI	≥27	21.9 (9)	6.44**	0.8 (1)	1.47	27.04
(b)	<27	3.4 (3)	-	0.5 (2)	-	6.18
(a)Use of	Yes	9.6 (5)	1.07	0.4 (1)	0.60	21.33
(b)Cigarette	No	9.0 (7)	-	0.7 (2)	-	12.00
All		9.2 (12)	-	0.6 (3)	-	15.33

@Incidence rate per 1,000 person year of observation.
Number in brackets refer to number of diabetes.
**P<0.01, 95% confidence interval 2.9-20.5.

TABLE 13.8. Predictive Value of Casual Post-Prandial Blood Glucose Value to 12-14 Years Worsening to Diabetes Mellitus in Men and Women with BMI Greater and Lesser than 27 Kg/m^2.

Item	Male		Female	
	BMI<27	BMI≥27	BMI<27	BMI≥27
Number in Population	266	142	358	134
Worsening to Diabetes	10	11	5	10
Non-diabetics	256	131	353	124
Sensitivity (%)	70	81.8	60	90
Specificity (%)	76.6	71	80.4	78.2
Positive Predictive Value (%)	10.4	19.1	4.2	25
Negative Predictive Value (%)	98.5	97.9	99.3	99

TABLE 13.9. Multiple Logistic Regression Analysis of the Relationship Between Eight Variables and 12-14 Year Progress to Diabetes.

Variable	Logistic Coefficient	Odds Ratio	Z-Test	95% Confidence Interval
Blood Glucose	1.24	11.96	6.1***	5.45-26.1
Gender	0.1660	1.40	0.9	-
Age	0.1694	1.40	0.9	-
Systolic BP	0.1254	1.28	0.6	-
Diastolic BP	0.3294	1.93	1.7	-
BMI	0.5701	3.13	3.2**	1.57-6.24
Cholesterol	0.0381	1.08	0.2	-
Smoking	0.0203	1.04	0.1	-

**P<0.01, ***P<0.001.

TABLE 13.10. Multiple Logistic Analysis of the Relationship Between Eight Variables and 12-14 Year Progress to Diabetes, in Index Group.

Variable	Logistic Coefficient	Odds Ratio	Z-Test	95% Confidence Interval
Gender	0.2680	1.71	0.1	-
Age	0.0239	1.05	0.1	-
Systolic BP	0.1353	1.31	0.0	-
Diastolic BP	0.3544	2.03	1.65	-
BMI	0.6893	3.96	2.9**	1.75-8.97
Cholesterol	-0.1279	0.77	-0.6	-
Smoking	0.0491	1.10	0.2	-

**P<0.01, ***P<0.001.

REFERENCES

1.Reid DD, Brett GZ, Hamilton PJS, et al: Cardiorespiratory disease and diabetes among middle aged male civil servants; a study of screening and intervention. Lancet 1974; 1:469-474.

2.Welborn TA, Cumpston GM, Cullen KJ et al: The prevalence of coronary heart disease and associated factors in an Australian rural community. Am J Epidemiol 1969; 89:521-536.

3.Hollnagel H, McCartney P: Relationship of fasting and post-load serum glucose to prevalence of ECG abnormalities in forty year old men. From the Glostrup Population Study. J Chron Dis 1979; 32:709-719.

4.Pyorala K, Punsar S, Siltanen P et al: Cardiovascular survey of policemen in Helsinki. Prevalence of electrocardiographic abnormalities (abstract). Scan J Clin Lab Inves 1969; 23 (suppl 108):53.

5.The North Karelia Project: Community control of cardiovascular disease. World Health Organization Regional Office for Europe, Copenhagen, 1981.

6.Reunanen A, Pyorala K, Punsar S, et al: Predictive value of ECG finding with respect to coronary heart disease mortality. Adv Cardiol 1978; 21:310-312.

7.Ducimetiere P, Eschwege J, Richard J, Claude J, Elgrishi I: Relationship of glucose tolerance to prevalence of ECG abnormalities and to annual mortality from cardiovascular disease: Results of the Paris Prospective Study. J Chron Dis 1979; 32:759-766.

8.Silva AD, Widner LK, Ziegler HW, Nissen C, Schwlizer W:

The Basle longitudinal Study: report on the relationship of initial glucose level to baseline ECG abnormalities, peripheral artery disease and subsequent mortality. J Chron Dis 1979; 32:797-803.

9.Matheson FAL, Varnam GS: Abnormal electrocardiograms in apparently healthy people. A long-term follow-up study. Circulation 1960; 21:196-203.

10.Gordon T, Moore FE, Shurtleff D, Dawber TR: Some methodological problems in the long-term study of cardiovascular disease -observations in the Framingham Study. J Chron Dis 1959; 10:186.

11.Rosenman RH, Friedman M, Straus R, et al.: A predictive study of coronary heart disease. JAMA 1964; 189:15.

12.Stamler J, Rhombery P, Schoenberger JA, et al.: Multivariate analysis of the relationship of seven variables to blood pressure: finding of the Chicago Heart Association Detection Project in Industry 1967-72. J Chron Dis 1975; 28:527.

13.Criqui MH, Barrett-Connor E, Austin M: Differences between respondents and non-respondents in a population-based cardiovascular disease study. Am J Epidemiol 1978; 108:367-372.

14.The Pooling Project Research Group: Relationship of blood pressure, serum cholesterol, smoking habit, relative weight and ECG abnormalities to incidence of major coronary events: Final report of the Pooling Project. J Chron Dis 1978; 31:201-306.

15.Hawthorne VM: Tuberculosis and cardio-respiratory mortality in the Renfrew District of Scotland. A report of

the trustees of the Renfrewshire King Edward Memorial Trust, 1985.

16.International Statistical Classification of Disease, Injuries and Cause of Death, Eighth Revision, WHO, Geneva, 1965:390-458.

17.WHO Epidem. Vit. Stat. Rep. 1967; 20:535.

18.WHO Chronicle: International work in cardiovascular diseases. 1969; 23:351.

19.World Health Stat. Annual (1969) Vol. 1 WHO, Geneva, 1972.

20.Fulton M, Adams W, Lutz W, Oliver MF: Regional variations in mortality from ischaemic heart disease in Britain. Br Heart J 1978; 40:563-568.

21.Hawthorne VM, Greaves DA, Beevers DG: Blood pressure in a Scottish Town. Br Med J 1974; 3:600-603.

22.Registrar General Scotland Annual Report part 1, Mortality Statistics, No. 118, HMO, Edinburgh 1972.

23.MOH Annual Report, Corporation of the City of Glasgow, 1972.

24.Howe GM: National Atlas of Disease Mortality in the United Kingdom, revised edition, the Royal Geography Society. London: Thomas Nelson and Sons, 1970.

25.Blackburn H: Ischaemic heart disease perspectives for prevention. Heart Bull 1971; 2:94-97.

26.Greaves DA, Hawthorne VM, McCartiney HN, Murdoch RM: The collaborative study on smoking in Scotland. A preliminary report on prevalence rates and values in 10,000 subjects by occupation and general population group. University of Glasgow, Dept. of Epidemiology and Preventive Medicine, 1973.

27.Miall WE, Brennan PJ: A pilot trial of treatment for mild hypertension, interim report of the Medical Research Council's Trial in Britain. Clin Sci Mol Med 1975; [suppl.] 48:165.

28.Truett J, Cornfield J, Kannel W. A multivariate analysis of the risk of coronary heart disease in Framingham. J Chron Dis 1967; 20:511.

29.Keen H, Rose GA, Pyke DA, Boyns D, Chlouverakis C, Mistry S:Blood sugar and arterial disease. Lancet 1965; 2:505-508.

30.Ostrander LD, Jr., Francis T, Jr., Hayner NS, Kjeisberg MO, Epstein FH: The relationship of cardiovascular disease to hyperglycaemia. Ann Intern Med 1965; 62:1188-1198.

31.Jarrett RJ, McCartney PM, Keen H:The Bedford Survey:Ten year mortality rates in newly diagnosed diabetics, borderline diabetics and normoglycaemic controls and risk indices for coronary heart disease in borderline diabetics. Diabetologia 1982; 22:79-84.

32.Epstein FH: Glucose intolerance and coronary heart disease incidence -recent observations. Horm Metab Res (Suppl 4) 174-180; 1974.

33.Framingham Study, An Epidemiological Investigation of Cardiovascular Disease (Section 29); Some Characteristics Related to the Incidence of Cardiovascular Disease and Death -Framingham Study , 16 Year Follow-up. Washington DC: U.S. Government Printing Office , 1970.

34.Goodkin G. Mortality Factors in Diabetes. J Occup Med 1975; 17:716.

35.Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H:Coronary heart disease risk and impaired glucose

tolerance. Lancet 1980; 1:1373-1376.

36.Stamler R, Stamler J eds. Asymptomatic hyperglycaemia and coronary heart disease. J Chron Dis 1979; 32:683-691.

37.Schroll M, Hagerup L: Relationship of fasting blood glucose to prevalence of ECG abnormalities and 10-yr risk of mortality from cardiovascular disease in men born in 1914: from Glustrop population studies. J Chron Dis 1972; 32:699-707.

38.Stenhouse N, Murphy BP, Welborn TA: Busselton population study: risk associated with asymptomatic hyperglycaemia. J Chron Dis 1972; 32:693-698.

39.Stamler R, Stamler J, Lindberg HA, et al.: Asymptomatic hyperglycaemia and coronary heart disease in middle aged men in two employed populations in Chicago. J Chron Dis 1979; 32:805-815.

40.Stamler R, Stamler J, Schoenberger JA et al.: Relationship of glucose tolerance to prevalence of ECG abnormalities and to 5-year mortality from cardiovascular disease: Findings of the Chicago Heart Association Detection Project in Industry. J Chron Dis 1979; 32:817-837.

41.Reunanen A, Pyorala K, Aromaa A, Maatela J, Knekt P:Glucose tolerance and coronary heart disease in middle-aged Finnish men: Social Insurance Institution's Coronary Heart Disease Study. J Chron Dis 1979; 32:747-756.

42.Pyorala K, Suvolainen E, Lehtovirta E, Punsar S, Siltanen P: Glucose tolerance and coronary heart disease: Helsinki Policemen Study. J chron Dis 1979; 32:729-745.

43.Fuller JH, McCartney P, Jarrett RJ, et al:

Hyperglycaemia and coronary heart disease: The Whitehall Study. J Chron Dis 1979; 32:721-728.

44.Hawthorne VM, Gilmour WH: The relationship of glucose to prevalence of ECG abnormalities at baseline and to 6-yr mortality in Scottish males aged 45-64 yr. J Chron Dis 1979; 32:787-796.

45.Eschwege E, Ducimetiere P, Papoz L, Claude JR, Richard JL: Blood glucose and coronary heart disease. Lancet 1980, 2:472.

46.Pyorala K, Savolainen G, Kaukola S, Haapakoski J: High Plasma Insulin As Coronary Heart Disease Risk Factor. In: Eschwege E, ed-Advances in Diabetes Epidemiology. IN SERM Symposium No:22. Amsterdam :Elsevier Biomedical Press, 1982:143.

47.Hickey N, Mulahy R, Daly L, Bourke G, Moriarty J: The relationship between blood glucose and prevalence of coronary heart disease: A study in the Republic of Ireland. J Chron Dis 1979; 32:767-772.

48.Farinoro E, Panico S, Oriente P, Mancini CM: The Olivetti Survey: Asymptomatic hyperglycaemia and ECG abnormalities at baseline. J Chron Dis 1979; 32:773-777.

49.Sakuma K, Hashimoto T, Maeda Y, Kusano S, et al.: Report of hyperglycaemia in middle-aged male Japanese National Railway Workers. J Chron Dis 1979; 32:779-786.

50.Gordon T, Kannel W B: Predisposition to atherosclerosis in the head, heart, and legs, The Framingham Study. JAMA 1972; 221:661.

51.Fuller J H, Shipley M J, Rose G: Stroke mortality and impaired glucose tolerance. The Whitehall Study. Diabetologia 1981; 21:272.

52.Sowder WT, Bond JO, William Jr., EH, Fleming EL: Man to man talk about women....and men. Florida state Board of Health. Monograph Series No. 10. Jacksonville. 1966.

53.Wingard DL: The sex differential in mortality rates: demographic and behavioral factors. Am J Epidemiol 1982; 115:205-216.

54.Wingard DL, Suareze L, Barrett-Connor E: The sex differential in mortality from all causes and ischaemic heart disease. Am J Epidemiol 1983; 117:165-172.

55.Waldron I: Why do women live longer than men? So Sci Med 1976; 10:349-62.

56.Retherford RD: The changing sex differential in mortality. Studies in population and urban demography £ 1. Greenwood Press, Westport. CT, 1975.

57.Burbank FUS: Lung cancer death rates begin to rise proportionately more rapidly for females than for males: a dose response effect? J Chron Dis 1972; 25:473.

58.Khosla T, Lowe Cr: Obesity and smoking habits by social class. Br J Prev Med 1972; 26:249-256.

59.Cahalan D, Cisin IH, Crossley HM. American drinking practices: national study of drinking behaviour and attitude. New Brunswick, NJ: Rutgers Centre of alcohol studies, 1968.

60.Hammand EC. Smoking in relation to the death rates of one million men and women. Nat Cancer Inst Monogr 1960; 19:127.

61.Johnson A: Sex differential in coronary heart disease: the explanatory role of primary risk factors. J Health Soc Behav 1977; 18:46-54.

62.Hammoud EI: Studies in fetal and infant mortality. Am J Public Health 1965; 55:1152-1163.

63.Teitelbam MS: Male and female components of perinatal mortality: international trends, 1901-63. Demography 1971; 8:541.

64.McMillen MM: Differential mortality by sex in fetal and neonatal death. Science 1979; 204:89-91.

65.Hamilton JB: The role of testicular secretions as indicated by the effects of castration in man and by studies of pathological conditions and the short life span associated with maleness. Recent Prog Horm Res 1948; 3:257.

66.Ricklefs RE: Fecundity, mortality and avian demography. Breeding Biology of Birds (Edited by D.S. Farner), PP. 370-390. National Academy of Science, Washington, 1973.

67.Caughley G: Mortality patterns in mammals. Ecology 1966; 47:906.

68.Stolnitz GJ: A century of international mortality trends: II. Pop Stud 1956; 10:17.

69.Tricomi V, Serr O, Solish C: The ratio of male to female embryos as determined by the sex chromatin. Am J Obstet Gynecol 1969; 79:504.

70.Donaldson RS, Kohl SG: Perinatal mortality in twins by sex. Am J Public Health 1965; 55:1411.

71.Scheinfeld A: The mortality of men and women. Scient Am 1958; 198:22.

72.Madigan FC. Are sex differentials biologically caused? Milbank Mem Q 1957; 35:202-223.

73.Hamilton JB, Mestler GE. Mortality and survival:

Comparison of eunuchs with intact men and women in a mentally retarded population. J Gerontol 1969; 24:395.

74.London WT, Rosenberg SE, Draper JW, Almy TP: The effect of oestrogens on arthriosclerosis. Am Intern Med 1961; 55:63.

75.Gerther MM, White PD: Coronary heart disease in young adults. Harvard University Press. Cambridge, 1954.

76.Furman RH. Endocrine factors in atherogenesis. In Atherosclerosis (Edited by F. G. Schottler and G.S. Boyd), PP. 375-409. Elsevier Amsterdam, 1969.

77.Berkson DM, Stamler J, Cohen DB. Ovarian function and coronary atherosclerosis. Clin Obstet Gynecol 1964; 7:504.

78.Ask-Upmark E: Life and death without ovaries. Acta Med Scand 1962, 172:129.

79.Parrish H, Carr CA, Hall DG, King TM: Time interval from castration in premenopausal women to development of excessive coronary atherosclerosis. Am J Obstet Gynecol 1967; 99:155.

80.Higano N, Robinson RW, Cohen WD: Increased incidence of cardiovascular disease in castrated women. N Engl J Med 1963; 268:1123.

81.Ritterband AB, Jaffe IA, Densen PM et al.: Gonadal function and the development of coronary heart disease. Circulation 1963; 27:237.

82.William TJ, Novak ER: Effect of castration and hysterectomy on the female cardiovascular system. Geriatrics 1963; 18:852.

83.Beavis ELG, Brown JB, Smith MA: Ovarian function after hysterectomy with conservation of the ovaries in

premenopausal women. J Obstet Gynaecol Br Commonw 1969; 76:969.

84.Baker MG: Psychiatric illness after hysterectomy. Br Med J 1968; 2:91.

85.Jenkins CD. Psychologic and social precursors of coronary disease. New Engl J Med 1971; 284:244-255.

86.Davis ME, Jones RJ, Jarolim C. Long-term oestrogen substitution and atherosclerosis. Am J Obstet. Gynecol 1961; 82:1003.

87.Stamler J, Gest MM, Turner JP: The status of hormonal therapy for the primary and secondary prevention of atherosclerotic coronary heart disease. Prog Cardiovasc Dis 1963; 6:220.

88.Veterans Administration Cooperative Urological Research Group. Treatment and survival of patients with cancer of the prostate. Surgery, Gynecol & Obstet 1967; 124:1011.

89.Blackard CE, Doe RP, Mellinger GT, Byar DP: Incidence of cardiovascular disease and death in patients receiving diethylstilbestrol for carcinoma of the prostate. Cancer 1970; 26:249.

90.Winkelstein W Jr., Stenchever MA, Lilienfeld AM: Occurrence of pregnancy, abortion, and artificial menopause among women with coronary artery disease: a preliminary study. J Chron Dis 1958; 7:273-86.

91.Kannel WB, Hjortland MC, McNamara PM, et al.: Menopause and risk of cardiovascular disease. The Framingham Study. Ann Intern Med 1976; 85:447-52.

92.The Coronary Drug Project. Finding leading to discontinuation of the 2.5 mg/day oesterogen group. JAMA

1973; 226:652-7.

93.Mann JI, Vessay MP, Thorogood M, et al.: Myocardial infarction in young women with special reference to oral contraceptive practice. Br Med J 1975; 2:241-249.

94.Heller RF, Jacobs HS: Coronary heart disease in relation to age, sex and the menopause. Br Med J 1978; 1:472-474.

95.Haynes SG, Feinleib M, Kannel WB: The relationship of psychosocial factors to coronary heart disease in the Framingham Study. III. Eight-year incidence of coronary heart disease. Am J Epidemiol 1980; 111:37-58.

96.Waldron I, Zyzanski S, Shekelle RB, et al.: The coronary prone behavior pattern in employed men and women. J Human Stress 1977; 3:2-18.

97.Rosenman RH, Friedman M: Association of specific behaviour pattern in women with blood and cardiovascular findings. Circulation 1961; 24:1173.

98.Maccoby EE, Jacklin CN: The Psychology of sex differences. Stanford University Press. Stanford, 1974.

99.Dentan RK. The Semai -A non-violent people of Malaya. Holt, Rinehart & Winston, New York, 1968.

100.Saario TN, Jacklin CN, Tittle CK. Sex role stereotyping in the public schools. Harvard Educ Rev 1973; 43:386.

101.Bart P: Why women see the future differently from men. Learning for tomorrow: The role of the future in education (Edited by A. Toffler), PP. 33-55. Random house, New York, 1972.

102.U'Ren MB: The image of women in textbooks. Women in

Sexist Society (Edited by V. Gormick and R.K. Moran) PP. 318-328. New American Library, New York, 1971.

103.Rosenman RH: The role of behavior patterns and neurogenic factors in the pathogenesis of coronary heart disease. Stress and the Heart (Edited by R.S. Eliot). PP. 123-141. Futura Publ, Mount Kisco, N.Y. 1974.

104.Bengtsson C: Ischaemic heart disease in women. Acta Med Scand 1973; (Suppl.):549.

105.Gove WR: Sex marital status and mortality. Am J Sociol 1973; 79:45.

106.Wilhelmsen L, Bengtsson C, Elmfeldt D, et al.: Multiple risk prediction of myocardial infarction in women as compared with men. Br Heart J 1977; 39:1179-1185.

107.Gordon T: Coronary heart disease in young women - incidence and epidemiology. In: Olive MF, ed. Coronary heart disease in young women. Edinburgh, London, New York: Churchill Livingstone 1978:12-19.

108.Kannel WB: Role of blood pressure in cardiovascular morbidity and mortality. Prog Cardiovas Dis 1974; 17:5-24.

109.Johansson S, Bergstrand R, Ulvenstam G, et al.: Sex differences in preinfarction characteristics and long-term survival among patients with myocardial infarction. Am J Epidemiol 1984; 119:610-623.

110.Dick TBS, Stone MC: Prevalence of three major risk factors in random sample of men and women and in patients with ischaemic heart disease. Br Heart J 1978; 40:617-26.

111.Friedman GD, Dules LG, Ury HK: Mortality in middle-aged smokers and non-smokers. N Engl J Med 1979; 300:213-217.

112.Paull O, Lepper MH, Phelon WH, et al.: A longitudinal

study of coronary heart disease. Circulation 1963; 23:20-31.

113.Morris JN, Kagan A, Pattison DC, Gardner MJ: Incidence and prediction of ischaemic heart disease in London busmen. Lancet 1966; 2:553-559.

114.Keys A, Taylor HL, Blackburn H, Brozek J, Anderson JT, Simonson E: Mortality and coronary heart disease among men studied for 23 years. Arch Intern Med 1971; 128:201-214.

115.Kannel WB, Gordon T, Schwartz MJ: Systolic versus diastolic blood pressure and the risk of coronary heart disease. The Framingham Study. Am J Cardiol 1971; 27:335-346.

116.Keys A, Arevonis C, Blackburn H, et al.: Probability of middle aged men developing coronary heart disease in 5 years. Circulation 1972; 45:815-828.

117.Wilhelmsen L, Wedel H, Tibblin G: Multivariate analysis of risk factors for coronary heart disease. Circulation 1973; 38:950-958.

118.Lebrach G, Schodel M, Seltzer M, Hart A: Assessing incidence and risk factors in myocardial infarction. Geriatrics 1975; 30:79-93.

119.Roseman RH, Shotz MS, Brand RJ: A study of comparative blood pressure measures in predicting risk of coronary heart disease. Circulation 1976; 54:51-58.

120.Lichenstein MJ, Shipley MJ, Rose G: Systolic and diastolic blood pressures as predictors of coronary heart disease mortality in the Whitehall study. BMJ 1985; 291:243-245.

121.Cotton CG, Nixon JM, Carpenter RG, Evans DW: Factors

discriminating men with coronary heart disease from healthy controls. Br Heart J 1972; 34:458.

122.Aagetverdal A: Systolic and diastolic blood pressure as predictors of coronary heart disease in middle aged Norwegian men. Br Med J 1987; 294:671-673.

123.Kleenbaum DG, Kupper LL, Cassel JC, Tyroler HA: Multivariate analysis of risk of coronary heart disease in Evan County, Georgia. Arch Intern Med 1971; 128:943-948.

124.Rabkin SW, Mathewson AL, Tate RB: Predicting risk of Ischaemic heart disease and cerebrovascular disease from systolic and diastolic blood pressure. Ann Intern Med 1978; 88:342-345.

125.Kannel WB, Wolf PA, Verter J, McNamara PM: Epidemiologic assessment of the role of blood pressure in stroke. JAMA 1970; 214:301-310.

126.Kannel WB, Dawber TR, Sorlie P, Wolf PA: Component of blood pressure and risk of artherothrombotic brain infarction: The Framingham Study. Stroke 1976; 7:327-331.

127.Evans PH: Relation of longstanding blood pressure levels to atherosclerosis. Lancet 1965; 1:516-519.

128.Medical Research Council Committee on chronic bronchitis questionnaire on respiratory symptom and instruction in its use. Medical Research Council, London, 1966.

129.Rose G, Blackburn H: Cardiovascular Survey Methods. WHO Monograph Series No. 56, Geneva, WHO 1968.

130.Rose GA, Holland WW, Crowley EA: A sphygmomanometer for epidemiologists. Lancet 1964; 1:296.

131.Rose GA: Standardization of observers in blood pressure measurement. Lancet 1965; 1:673.

132.Annon W, Isherwood DM: An automated method for the direct determination of total serum cholesterol. J Med Lab Tech 1969; 26:202-211.

133.Kaddish AH, Little RA, Sternberg JC:A new and rapid method for the determination of glucose by measurement of rate of oxygen consumption. Clin Chem 1968; 14:116-131.

134.Garthur (London) LTD. an introduction to routine lung function tests with the Gathur Vitalograph Brochure No. J49A. 1st edition, London 1963.

135.Manual of the International Statistical Classification of Disease, Injuries and Cause of Death. Ninth Revision, Genova: World Health Organization 1977.

136.Annual Report of the Regitrar General for Scotland, 1979. Edinburgh Her Majesty's Stationary Office.

137.Elveback LR: How high is high? A proposed alternative to the normal range. Mayo Clin Proc. 1972; 47:93.

138.Dixon WJ: Biomedical Data Processing (BMDP) Statistical Software, University of California Press, 1983.

139.Walker SH. and Duncan DB: Estimation of the probability on events as a function of several independent variables. Biometrika 1967; 54:167-179.

140.Isles CG, Walker LM, Beevers GD et al: Mortality in patients of Glasgow blood pressure clinic. Journal of Hypertension 1986, 4:141-156.

141.Kessler II:Mortality experience of diabetic patients. Am J Med 1971; 51:715-724.

142.Pell S, D'Alonzo CA: Factors associated with long-term survival of diabetics. JAMA 1970; 214:1833-1840.

143.Jarrett RJ, Keen H:Diabetes and atherosclerosis In: Keen H, Jarrett J (eds) Complications of Diabetes. Edward Arnold, London 1975; PP. 179-204.

144.West KM: Epidemiology of diabetes and its vascular lesions. New York:Elsevier, 1978; 159.

145.Liebow IM, Hellerstein HK:Cardiac complications of diabetes mellitus. Am J Med 1949; 7:660-670.

146.Katz LN, Stamler J:Experimental atherosclerosis. Springfield: Charles C.Thomas 1953.

147.Camerini-Du'valos, Cole HS (Eds):Vascular and neurological changes in early diabetes. New York: Academic Press 1973.

148.International Collaborative Group:Summary and joint discussion.J chron Dis 1979; 32:829-837.

149.Ostrander LD Jr., Lamphiear DE:Coronary risk factors in a community:Findings in Tecumseh, Michigan. Circulation 1976; 53:152-156.

150.Kannel WB, McGee DL:Diabetes and cardiovascular risk factors:The Framingham Study. Circulation 1979; 59:598-612.

151.Ostrander LD Jr., Lamphiear DE, Block WD, Williams GW, Carman WJ:Physiological variables and diabetic status:Findings in Tecumseh Michigan. Arch Intern Med 1980; 140:1215-1219.

152.Snapper I:Chinese Lessons to Western Medicine. New York:Interscience 1941.

153.Shaper AG, Lee KT, Scott RF, Goadale F, Thomas WA:Chemico-anatomical studies in the geographic pathology of atherosclerosis: Comparison of adipose tissue fatty acids and plasma lipids in diabetics from East Africa and

the United States with different frequencies of myocardial infarction. Am J Cardiol 1962; 10:390-399.

154.McGill HC Jr. (Ed):Geographic pathology of atherosclerosis. Baltimore: Williams & Wilkins, 1968.

155.Stamler J, Pick R, Katz LN: Influence of thyroid pancreatic and adrenal hormones on lipid metabolism and atherosclerosis in animals. In: Hormones and Atherosclerosis. Proc. Conf. Pincus G (Ed) New York:Academic Press, 1959.

156.Mantel N, Haenszel W:Statistical aspect of the analysis of data from retrospective studies of disease. Journal of National Cancer Institute 1959; 22:719-748.

157.Gordon T: Glucose tolerance of adults, United States, 1960-68: Diabetes prevalence and results of glucose tolerance test, by age and sex. National Centre for Health Statistics. Vital and Health Statistics, Series 1 No.2. Washington, DC: U.S. Government Printing Office, 1964.

158.Hayner NS, Kjelsberg MO, Epstein FH, Francis T:Carbohydrate tolerance and diabetes in a total community, Tecumseh, Michigan.1.Effects of age, sex and test condition on one hour glucose tolerance in adults. Diabetes 1965; 14:413.

159.Phillips N, Duffy T:Effect of age, hours since last food, time of day, and ketonuria on one-hour glucose tolerance. Health Ser Resp 1972; 87:649.

160.Andres R: Aging and diabetes. Med Clin North Am 1971; 55:835.

161.O'Sullivan JB: Age gradient in blood glucose levels: magnitude and clinical implications. Diabetes 1974;

23:713.

162.Garcia MJ, McNamara PM, Gordon T, et al.:Morbidity and mortality in diabetics in the Framingham population. Diabetes 1974; 23:105-111.

163.Gordon T, Castelli WP, Hjortland MC, et al.:Diabetes blood lipids, and the role of obesity in coronary heart disease risk for women. The Framingham Study. Ann Int Med 1977; 87:393-397.

164.Heyden S, Heiss G, Bartel AG, et al.:Sex differences in coronary mortality among diabetics in Evan County, Georgia. J Chron Dis 1980; 33:265-73.

165.Kannel WB, McGee DL:Diabetes and glucose tolerance as risk factor for cardiovascular disease:The Framingham Study. Diabetes Care 1979; 2:120-126.

166.Hayward RE, Lucera BC: An investigation into the mortality of diabetics. J Instit Actuar 1965; 91:286-336.

167.Welborn TA, Wearne K: Coronary heart disease incidence and cardiovascular mortality in Busselton with reference to glucose and insulin concentrations. Diabetes care 1979; 2:154-160.

168.Fuller J, Shipley M, Rose G, Jarrett RJ, Keen H: Mortality from coronary heart disease and stroke in relation to degree of glycaemia: The Whitehall Study. Br Med J 1983; 287:867-870.

169.Butler WJ, Ostrander LD Jr., Carman WJ, Lamphiear DE: Mortality from coronary heart disease in the Tecumseh Study. Long-term effect of diabetes mellitus, glucose tolerance and other risk factors. Am J Epidemiol 1985; 121:541-547.

170.Yano K, Kagan A, McGee D, Rhoads GG: Glucose

intolerance and nine-year mortality in Japanese men in Hawaii. Am J Med 1982; 72:71-80.

171.National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; 28;1039.

172.WHO Expert Committee on Diabetes Mellitus: Second report. WHO Tech Rep Ser No. 645, 1980.

173.Stamler J, Stamler R, Rhomberg P, et al.: Multivariate analysis of the relationship of six variables to blood pressure: Finding from Chicago Community Survey, 1965-1971. J Chron Dis 1975; 28:499-525.

174.Jarrett RJ, Keen H, McCartney M, et al.:Glucose tolerance and blood pressure in two population samples: Their relation to diabetes mellitus and hypertension. Int J Epidemiol 1978; 7:15-24.

175.Nilsen R, Persson G:Smoking habits in diabetics. Lancet 1972; 1:1283-1284.

176.Czyzyk A, Krolewiski AS:Is cigarette smoking more frequent among insulin-treated diabetics? Diabetes 1976; 25:717-718.

177.Verbrugge LM: Sex differentials in morbidity and mortality in the United States. Soc Biol 1976; 23:275-96.

178.Jarrett RJ.:Diabetes and heart: Coronary heart disease. Clin Endocrin Metab 1977; 6:389-402.

179.Keen H: Factors influencing the progress of artheriosclerosis in diabetics. Acta Diabetol Lat 1971; 8(Suppl.):444.

180.Keen H, Jarrett RJ: The effect of carbohydrate tolerance on plasma lipids and artheriosclerosis in man.

In: Atherosclerosis. Jones RJ (ed.). New York: Springer, P. 453, 1976.

181.Thomas WA, Lee KT, Rabin ER: Fatal acute myocardial infarction in diabetic patients. Arch Intern Med 1956; 98:489-94.

182.Clawson BJ, Bell ET: Incidence of fatal coronary disease in non-diabetic and in diabetic patients. Arch Pathol 1949; 48:105-6.

183.Gordon T, Castelli WP, Hjortland MC, et al.: Predicting coronary heart disease in middle-aged and older persons. The Framingham Study. JAMA 1977; 238:497-9.

184.Stamler J: Artheriosclerosis coronary heart disease. In: Sussman KE, Metz RJS, eds. Diabetes mellitus, 4th ed. New York: American Diabetes Association, 279-41, 1975.

185.Epstein FH: Glucose intolerance and coronary heart disease incidence recent observations In: Lipid Metabolism, Obesity and Diabetes Mellitus: impact upon atherosclerosis. Hormone and Metabolic Research. Suppl. Series No. 4 Levine R. Pfeiffner EF (eds.). Stuttgart. Thieme. 1974.

186.Pan WH, Cedres LB, Liu K, et al.: Relationship of clinical diabetes and asymptomatic hyperglycaemia to risk of coronary heart disease mortality in men and women. Am J Epidemiol. 1986; 123:504-516.

187.Bailey RR, Beaven DW. Diabetes mellitus and myocardial infarction. Aust Ann Med 1968; 17:312-4.

188.Soler NC, Bennett MA, Pentecost BL, et al. Myocardial infarction in diabetics. Q J Med 1975; 44:125-32.

189.Aarseth S: Cardiovascular-renal disease in diabetes mellitus: A clinical study. Acta Med Scand 1953; Suppl

281:1-252.

190.Krolewski AS, Czyzk A, Janeczko D et al.: Mortality from cardiovascular disease among diabetes. Diabetologia 1977; 13:345-50.

191.Barrett-Connor E, Wingard D: Sex differential in ischaemic heart disease mortality in diabetics. A prospective population-based study. Am J Epidemiol 1983; 118:489-496.

192.Liu, Stamler J, Stamler R, et al.: Methodological problems in characterising an individual's plasma glucose level. J Chronic Dis 1982; 35:475-85.

193.Robkin SW, Mathewson FA, H su' PH: Relation of body weight to development of ischaemic heart disease in a cohort of young North American men after a 26 year observation period. The Manitoba Study .Am J Cardiol 1977; 39:452.

194.Robertson TL, Kato H, Gordon T, et al.: Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan , Hawaii and California. Am J Cardiol 1977; 39:244.

195.Chapman JM, Coulson AH, Clark VA, Borun ER: The differential effect of serum cholesterol, blood pressure and weight on the incidence of myocardial infarction and angina pectoris. J Chron Dis 1971; 23:631.

196.Petitti DB, Wingerd J, Pellegrin F, Ramcharan S: Risk of vascular disease in women. Smoking, oral contraceptives, noncontraceptive oestrogens, and other factors. JAMA 1979; 242:1150.

197.Heyman A, Karp HR, Heyden S, et al.: Cerebrovascular

disease in the biracial population of Evan County, Georgia. Arch Intern Med 1971; 128:949-955.

198.Chiang BN, Perlman LV, Epstein FH: Overweight and hypertension. A review. Circulation 1969; 39:403.

199.Kannel WB, Gordon T, Castelli WP: Obesity, lipids, and glucose intolerance. The Framingham Study. Am J Clin Nutr 1979; 32:1238.

200.Garrison RJ, Wilson PW, Castelli WP, Feinleib M, Kannel WB, McNamara PM: Obesity and lipoprotein cholesterol in the Framingham offspring study. Metabolism 1980; 29:1053.

201.Noppa H, Bengtsson C, Bjorntorp P, Smith U, Tibblin E: Overweight in women-metabolic aspects. The population study of women in Gotenborg 1968-1969. Acta Med Scan 1978; 203:1359.

202.Leren P, Askevald EM, Foss OP, et al.: The Oslo Study. Cardiovascular disease in middle aged and young Oslo men. Acta Med Scan (Supp 588):1977.

203.Stamler J:Overweight, hypertension, hypercholesterolemia and coronary heart disease In: Mancini M, Lewis B, Contaldo F, eds. Medical complications of obesity. London: Academic Press, 191-216, 1979.

204.Noppa H:Body weight change in relation to incidence of ischaemic heart disease and change in risk factors for ischaemic heart disease. Am J Epidemiol 1980; 111:693.

205.Ashley FW, Kannel WB:Relation of weight change to changes in atherogenic trait: The Framingham Study. J Chron Dis 1974; 27:103.

206.Joslin EP: The prevention of diabetes mellitus. JAMA 1921; 76:79-84.

207.John HF: A summary of findings in 1100 glucose tolerance estimation. Endocrinology 1929; 13:388-392.

208.Zimmet P: Type 2 (non-insulin-dependent) diabetes -an epidemiologic overview. Diabetologia 1982; 22:399-411.

209.Hubert HB, Feinleib M, McNamara PM, et al.: Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation 1983; 67:968-77.

210.Bjorntorp P: Obesity and risk of cardiovascular disease. Acta Med Scan 1985; 218:145-7.

211.Garrison RJ, Feinlib M, Castelli WP, McNamara PM: Cigarette smoking as a confound of the relationship between relative weight and long-term mortality: The Framingham Study. JAMA 1983; 249:199-202.

212.Lew EA, Garfin Kel L: Variation in mortality by weight among 750,000 men and women. J Chron Dis 1979; 32:563-576.

213.Jarrett RJ, Shipley MJ, Rose G: Weight and mortality in the Whitehall Study. Br Med J 1982; 285:535-537.

214.Sorlie P, Gordon T, Kannel WB: Body build and mortality: The Framingham Study. JAMA 1980; 243:1828-31.

215.Larsson B, Bjorntorp P, Tibblin G: The health consequences of moderate obesity. Int J Obs 1981; 5:97-116.

216.Garn SM, Hawthorne VM, Pilkington JJ, Pesick SD: Fatness and mortality in the west of Scotland. Am J Clin Nutr 1983; 38:313-319.

217.Keys A: Seven Countries: A multivariate analysis of death and coronary heart disease, Cambridge, Massachusetts, and London, England: Harvard University Press, 1980.

218.Keys A: Overweight, obesity, coronary heart disease and mortality. Nutr Rev 1980; 38:297-307.

219.Hubert HB: The nature of relationship between obesity and cardiovascular disease. Int J Cardiol. 1984; 6:268-74.

220.Barrett-Connor EL: Obesity, atherosclerosis, and coronary artery disease. Ann Intern Med 1985; 103:1010-1019.

221.Keys A, Aravanis C, Blackburn H, et al: Coronary heart disease, overweight and obesity as risk factors. Ann Intern Med. 1972; 77:15-27.

222.Herdon G. Causes of excess mortality in man. Acta Genet 1952; 3:351-75.

223.Enterline PE: Causes of death responsible for recent increases in sex mortality differentials in the United States. Milbank Mem Fund Q 1961; 39:312-28.

224.Yerushalmy J. Factors in human longevity. Am J Publ Health 1963; 53:148.

225.Report of the Royal College of Physicians. Smoking and health now. Pitman, London, 1971.

226.Epstein FH, Ostrander SD, Johnson BC, et al.: Epidemiologic studies of cardiovascular disease in total community- Tecumseh, Michigan. Ann Intern Med 1965; 62:1170-1187.

227.Stamler J, Berkson DM, Morjonner L, et al.: Epidemiologic studies on atherosclerosis, coronary heart disease, causative factors and consequent preventive approaches. Prog Biochem Pharmacol 1968; 4:30-49.

228.Doyle JT, Heslin AS, Hilleboe HE, Formel PF: Early diagnosis of Ischaemic heart disease. N Eng J Med 1959; 261:1096-1101.

229.Build and blood pressure study, 1959 Vol 1. Chicago, Society of Actuaries, 1959.

230.Oberman A, Harlan WR, Smith M, Graybiel A:The cardiovascular risk associated with different levels and types of elevated blood pressure. Minn Med 1969; 52:1283.

231.Friedberg CK: Disease of the heart, 3rd ed. Philadelphia W.B. Saunders Co., 1966 P 1475.

232.Harrison TR: Principal of Internal Medicine, 7th ed. New York, McGraw-hill, 1974, P 1236.

233.Report of the joint National Committee on detection, evaluation and treatment of high blood pressure. Arch Intern Med 1980; 140:1280-1285.

234.Finfillman S, Worcel M, Agrest A: Hemodynamic pattern in essential hypertension. Circulation 1965; 31:356-368.

235.Frochlich ED, Tarazi RC, Dustan HP: Reexamination of the hemodynamics of hypertension. Am J Med Sci 1969; 257:9-23.

236.Brand RJ, Rosenman RH, Soltz RT, Friedman M: Multivariate prediction of coronary heart disease in the Western Collaborative Group Study compared to the finding of Framingham Study. Circulation 1976; 53:348-355.

237.Page LB, Sidd JJ: Medical management of primary hypertension (part 1). N Engl J Med 1972; 287:960-967.

238.Veterans Administration Cooperative Study Group on Antihypertensive Agents. Effect of treatment on morbidity in hypertension: Results in patients with diastolic blood pressure averaging 115 through 120 mmHg. JAMA 1967; 202:1028.

239.Randall OS: Effect of arterial compliance on systolic

blood pressure and cardiac function. Clin Exp Hypertens [A] 1982; 4:1045-57.

240.Cambient F, Chretien JM, Ducimetiere P, Guize L, Richard JL: Is the relationship between blood pressure and cardiovascular risk depend on body mass index. Am J Epidemiol 1985; 122:434-42.

241.Kannel WB: Current status of the epidemiology of brain infarction associated with occlusive arterial disease. Stroke 1971; 2:295-318.

242.Chapman JM, Reeden LG, Rowen ER, Clark VA, Coulson AH: Epidemiology of vascular lesions affecting the central nervous system: The occurrence of stroke in a sample population under observation for cardiovascular disease. Am J Public Health 1960; 56:191-201.

243.Berkson DM, Stamler J: Epidemiological findings on cerebrovascular disease and their implications. J Atheroscler Res 1965; 5:189-202.

244.Gubner RS: Life expectancy in the young hypertensive. In: Brest AN, Moyeer JH, eds. Hypertension: Recent advances. Philadelphia: Lea & Febiger, 1961: 18-23.

245.Gubner RS: Systolic hypertension. A pathogenetic entity. Significance and therapeutic considerations. Am J Cardiol 1962; 9:773-76.

246.Kannel WB, Dawber TR: Hypertension as an ingredient of a cardiovascular risk profile. Br J Hosp Med 1974; 11:508-23.

247.Wolf PA: Hypertension as a risk factor for stroke. Whisnant JP, Sandok BA, eds. Ninth Princeton Conference, Cerebral Vascular Disease. New York. Grune and stratton, 1975: 105-13.

248.Kannel WB, Wolf PA, McGee DL, Dawber TR, McNamara P, Castelli WP: Systolic blood pressure, arterial rigidity and risk of stroke. The Framingham Study. JAMA, 1981;245:1225-29.

249.Fisher CM: The ascendancy of diastolic blood pressure over systolic: Lancet, 1985: 1349-50.

250.MacMahon B, Pugh TF: Epidemiology: Principles and Methods. Boston, Little Brown and Co. 1970, PP 218-220, 224-226.

251.Modan B: Some methodological aspects of a retrospective follow-up study. Am J Epidemiol 1965; 82:297-304.

252.Sims AC: Importance of a high tracing rate in long-term medical follow-up studies. Lancet 1973; 2:433-435.

253.Theodore A, Berger AG, Palmer CE: Follow-up study of tuberculosis in former student nurses. J Chronic Dis 1956; 3:499-520.

254.Boice JD: Follow-up methods to trace women treated for pulmonary tuberculosis. Am J Epidemiol 1978; 107:127-139.

255.Redmond CK, Smith EM, Lioyd JW et al.:Long-term mortality study of steelworkers. III. Follow-up. J Occup Med 1969; 11:513-521.

256.Paffenbarger RS, Wing AL, Hyde RT: Physical activity as an index of heart attack risk in college alumni. Am J Epidemiol 1978; 108:161-175.

257.Dawber Tr, Kannel WB, Lyell LP: An approach to longitudinal studies in a community: The Framingham study. Ann NY Acad Sci 1963; 107:539-556.

258.Acheson ED: Medical record linkage. London, Oxford University Press, 1967.

259.Collins Cobuild English Language Dictionary. The University of Birmingham, Collins Publishers, London 1987.

260.Dunn HL: Record linkage. Am J Public Health 1946; 36:1412.

261.Newcombe HB, Kennedy JM, Axford SJ, James AP: Automatic linkage of vital records. Science 1959; 130:954.

262.Skegg DCG: Medical record linkage. In: Monitoring for drug safety, Inman WHD (ed) 1980, pp 337-348, Lancaster, MTP press.

263.Jones RB, Hedley AJ: Improving the quality of data in a computerised patient master index: implications for costs and patient care. Effective Health Care 1984; 2:97-102.

264.Jones SJ, Hedley AJ, Curtis B, Allison SP: Do we need thyroid follow-up registers? A cost-effective study. Lancet 1982:1229-1233.

265.Waterhouse J, Muir C, Correa P et al: Cancer incidence in five continents. Volume 3. Lyon, France, IARC, 1976.

266.Heasman MA, Clark JA: Medical Record Linkage in Scotland. Health Bull. (Edinb.) 1979; 37:97-103.

267.Graham PA, Wallace J, Welsby E et al: Evaluation of postal detection of registrable blindness. Br J Prev Soc Med 1968; 22:238-241.

268.Bahn AK: Psychiatric case register conference, 1965. Public Health Rep 1966; 81:748-54.

269.Gordis L, Lilienfield A, Rodriguez R: A community wide study of acute rheumatic fever in adults. JAMA 1969; 210:862-65.

270.Feller I, Crane KH: National burn information exchange. Surg Clin North Am 1970; 50:1425-36.

271.Pole DJ: Myocardial infarction incidence: Methods, validity and preliminary experience of a coronary register. Med J Aust 1972; 2:1481-84.

272.Whitig L: The central registry for child abuse cases: Rethinking basic assumptions. Child Welfare 1977; 56:761-67.

273.Charters AC, Bailey JA: Experience with a simplified trauma registry: Profile of trauma at a university hospital. J Trauma 1979; 19:13-17.

274.Goldberg J, Gelfand HM, Levy PS: Registry evaluation methods: A review and case study. Epidemiologic Review 1980; 2:210-220.

275.Baldwin JA: Medical record linkage. Medicine 1974; 35:2048-2050.

276.Department of Health and Social Security and Scottish Home and Health Department, (1973). Security of the census of population. Cmnd 5365. London, HMSO.

277.Scottish Home and Health Department (1978). Confidentiality of medical records held on computers. NHS Circular 1978 (GEN) 23.

278.Lockwood E: Accuracy of Scottish hospital morbidity data. Br J Prev Soc Med 1971; 25:76-83.

279.Martini CJM, Hughes AD, Patton V: A study of the validity of the hospital activity analysis information. British Journal of Preventive and Social Medicine 1976; 30:180-186.

280.Patel AR, Gray G, Lang GD, Baillie FGH, Fleming L,

Wilson GM: Scottish hospital morbidity data-2. An attempt to improve the standard of diagnositic entries and records in a medical unit. Health Bull (Edinb) 1976; 34:221-227.

281. Patel AR, Gray G, Lang GD, Baillie FGH, Fleming L, Wilson GM: Scottish hospital morbidity data-3. some suggestions for improvement of the accuracy. Health Bull (Edinb) 1976; 34:227-228.

282. Coid DR: Assessment of cerebrovascular morbidity in Fife. Public Health 1988, 102:141-145.

283. Heliovaraa M, Reunanen A, Aromaa A, Knekt P, Aho K, Suhonen O: Validity of hospital discharge data in a prospective epidemiological study on stroke and myocardial infarction. Acta Med Scand 1984; 216:309-15.

284. Alderson MR, Meade TW: Accuracy of diagnosis on death certificates compared with that in hospital records. Br J Prev Soc Med 1967; 21:22-29.

285. Beadenkopf WG, Abrams M, Daoud A et al: An assessment of certain medical aspects of death certificate data for epidemiologic study of arteriosclerotic heart disease. J Chron Dis 1963; 16:249-262.

286. Britton M: Diagnostic error discovered at autopsy. Acta Med Scand 1974; 196:203-210.

287. Dorn HF, Cutler SS: Comparison of death certificates and case reports in morbidity from cancer in the United States. Pub Health Mon 1959; 56:117-124.

288. Fedrick J, Butler NR: Accuracy of registered causes of neonatal deaths in 1958. Br J Prev Soc Med 1972; 26:101-105.

289. Gwynne JF: The unreliability of death certificates. N Z Med J 1974; 80(526):336.

290.Heasman MA, Lipworth 1: Accuracy of certification of cause of death: Studies on medical and population subjects. HMSO. London No 20, 1966.

291.James G, Patton RE, Heslin AS: Accuracy of cause of death statements on death certificates. Pub Health Rep 1955; 70(1):39-51.

292.Paton BC: The accuracy of diagnosis of myocardial infarction: A clinicopathologic study. Am J Med 1957; 23:761-68.

293.Bonser GM, Thomas GM: An investigation of the validity of death certification of cancer of lung in leeds. Br J Cancer 1959; 13(1):1-12.

294.Rosenblatt MB, Teng PK, Kerpe S, et al: Causes of death in 1,000 consecutive autopsies. New York State J Med Sep. 15, 1971; 2189-2193.

295.Flory C, Du V, Senter MG, et al: A study of validity of diagnosis of stroke in mortality data II: Comparison by computer of autopsy and clinical records with death certificates. Am J Epi 1969; 89(1):15-24.

296.Kuller L, Blanch T, Havlik R: Analysis of validity of cerebrovascular disease mortality statistics in Maryland. J Chron Dis 1967; 20:841-51.

297.Schoenberg BS and Powell JM: Statistics on stroke: A pilot study of the clinical evidence justifying the reporting of stroke on death certificates in Alameda County, California. Cal Med 1968; 109(1):19-23.

298.Gorham LW: A study of pulmonary embolism. Part 1A. Clinicopathological investigation of 100 cases of massive embolism of the pulmonary artery: Diagnosis by physical

signs and differentiation from acute myocardial infarction. Arch Int Med 1961; 108:8.

299.Hook EB, Farina MA, Hoff MB: Death certificate reports of cardiovascular disorders in children: Comparison with diagnoses in a paediatric cardiology registry. J Chron Dis 1977; 30:383-91.

300.Khoury SA: Death certificate and tuberculosis register cards. A correlation study of 108 cases. Am Rev Respir Dis 1971; 104(6):936-37.

301.McCarthy PD, Walsh D: Suicide in Dublin: I. The under reporting of suicide and the consequences for national statistics. Br J Psychiatry Apr 1975; 126:301-8.

302.Walsh G, Walsh D, Whelan B: Suicide in Dublin: II. The influence of some social and medical factors on coroner's verdicts. Br J Psychiatry Apr 1975; 126:309-12.

303.Ross D, Kreitman N: A further investigation of differences in the suicide rates of England and Wales and Scotland. Br J Psychiatry Dec 1975; 127:575-82.

304.Miller RW: Childhood cancer and congenital defects. A study of United States death certificates during the period 1960-1966. Pediatr Red 1969; 3(5):389-97.

305.Rossman I: True incidence of pulmonary embolization and vital statistics. JAMA 1974; 230(12):1677-79.

306.Mitchell RS, Maisel JC, Dart GA, et al: The accuracy of death certificate in reporting cause of death in adults: With special reference to chronic bronchitis and emphysema. Am Rev Resp Dis 1971; 104:844-50.

307.Murphy T: Certification of death from cancer of the uterus. J Irish Med Assn 1967; 60(363):385-88.

308.Rose G, Oxon DM: Errors in the classification of fatal

pericarditis. Lancet 1966; 851.

309.Gittelsohn A, Senning J: Studies on the reliability of vital and health records: I. Comparison of cause of death and hospital record diagnoses. Am J Public Health 1979; 69:680-89.

310.Hole DJ, Clarke JA, Hawthorne VM, Murdoch RM: Cohort follow-up using computer linkage with routinely collected data. J Chron Dis 1981; 34:291-297.

311.Hedley AJ, McMaster W: Use of the National Health Service Central Register for medical research purposes. Health Bulletin 1988; 46:63-68.

312.Angus J, Cameron L, Finlayson CF, Hopkins RT, Martin KB, Scott JH: The Tayside master patient index. Dundee: Tayside Health Board 1978.

313.Hedley AJ, Alexander EA, Innes G: Patient identification and documentation of causes of death in a follow-up register. Health Bulletin 1977; 35:73-77.

314.Jones R, Hedley A, Gale E: Identification of diabetic patients treated with insulin or oral hyperglycaemics within a defined population. Community Medicine 1986; 8:104-10.

315.O'Sullivan JB, Mahan CM: Blood sugar levels, glycosuria, and body weight related to development of diabetes mellitus. JAMA 1965; 194:117-122.

316.Diabetes Survey Working Party: A diabetes survey. Br Med J 1962; 1:1497-1503.

317.Diabetes Survey Working Party: Five-year follow-up report on Birmingham Diabetes Survey of 1962. Br Med J 1970; III:301-305.

318.Diabetes Survey Working Party: Ten-year follow-up report on Birmingham Diabetes Survey of 1961. Br Med J 1976; II:35-57.

319.O'Sullivan JB, Mahan CM: Prospective study of 352 young patients with chemical diabetes. N Engl J Med 1968; 278:1038-1041.

320.Stowers JM: Treatment of chemical diabetes with chlorpropamide and the associated mortality. Adv Metab Disord 1973; [Suppl.] 2:549-555.

321.Feldman RF, Craword D, Elashoff R, Glass A: Progress report on the prophylactic use of oral hyperglycaemic drugs in asymptomatic diabetes: neurovascular studies. Adv Metab Disord 1973; [Suppl.] 2:557-567.

322.Carlstrom S, Lundquist A, Lundquist I, Norden A, Schersten B, Wollmark G: Studies in subjects with positive post-prandial Clinistix test. Acta Med Scand. 1971; 189:415-422.

323.Kobberling J, Kattermann R, Arnold A: Follow-up of "non-diabetic" relatives of diabetics by re-testing oral glucose tolerance after 5 years. Diabetologia 1975; 11:451-456.

324.Jarrett RJ, Keen H: Hyperglycaemia and diabetes mellitus. Lancet 1976; II:1009-1012.

325.Jarrett RJ, Keen H, Fuller JH, McCartney M: Worsening to diabetes in men with impaired glucose tolerance ("borderline diabetes"). Diabetologia 1979; 16:25-30.

326.O'Sullivan JB, Hurwitz D: Spontaneous remissions in early diabetes mellitus. Arch Int Med 1966; 117:769-774.

327.Merrell M, Shulman LE: Determination of prognosis in chronic disease, illustrated by systemic lupus

erythmatosus. J Chron Dis 1955; 1:12-32.

328.Ingelfinger JA, Mosteller F, Thibodeau LA, Ware JH: Biostatistics in clinical medicine. Macmillan Publishing Co., INC., New York, Toronto, London.

329.Epstein FH: Hyperglycaemia. A risk factor in coronary heart disease. Circulation 1967; 36:609.

330.Keen H, Jarrett RJ: Modern concepts in the diagnosis of diabetes. In: The management of stable adult diabetes. ed. C. Weller; Chapter 1, P 3. Thomas, Springfield, III. 1969.

331.Dornan C, Fowler G, Mann JI, Marhus A, Thorogood M: A community study of diabetes in Oxfordshire. J R Coll Gen Pract 1983; 37:151-155.

332.Hatano S: Observer variations in the diagnosis of stroke. WHO Collaborative Study on the Control of Stroke in the Community. JPN Heart J 1977; 18:171-177.

333.Cameron HM, McGoogon ES, Clarke J, Wilson B: Trends in hospital necrospy rate: Scotland 1961-74. Br Med J 1977; 1:1577-1580.

334.Kirkendall WM, Burton AC, Epstein FH, et al.: Recommendations for human blood pressure determination by sphygmomanometer. Circulation 1967; 36:980-988.

335.Uemura K, Pisa Z: Recent trends in cardiovascular disease mortality in 27 industrialized countries. World Health Statistical Quarterly 1985; 38:142-162.

336.Haberman S, Capildeo R, Rose FC:The changing mortality of cerebrovascular disease. QJ Med 1978; 47:71-88.

337.Acheson RM: Mortality from cerebrovascular accidents and hypertension in the Republic of Ireland. Br J Prev Soc

Med 1960; 14:139-147.

338.Recent trends in mortality from cerebrovascular disease. Stat Bull Metropol Life Ins Co 1975; 56(11):2-4.

339.Soltero I, Liu K, Cooper R. Stamler J, Garside D: Trends in mortality from cerebrovascular diseases in the United States,1960 to 1975. Stroke 1978; 9:549-558.

340.Tanaka H, Tanaka Y, Hayashi M, et al.: Secular trends in mortality for cerebrovascular diseases in Japan ,1960 to 1976. Stroke 1982; 13:574-581.

341.Whisnant JP: The decline of stroke. Stroke 1984; 15:160-8.

342.Alfredsson 1, VonArbin M, DeFaire U: Mortality from and incidence of stroke in Stockholm. BMJ 1986; 292:1299-1303.

343.Anonymous: Why has stroke mortality declined? [Editorial]. Lancet 1983; 1:1195-6.

344.Soltero I, Cooper R: Improved hypertension control and decline in cardiovascular mortality. Comper Ther 1980; 6:60-64.

345.Levy RT, Moskowitz J:Cardiovascular Research: Decade of progress, a decade of promise. Science 1982; 217:121-9.

346.Bonita R, Beaglehole R: Does treatment of hypertension explain the decline in mortality from stroke. Br Med J 1986; 292:191-192.

347.Jackson RT, Beaglehole R, Stewart AW: Blood pressure levels and treatment of hypertension in Auckland , NZ Med J 1983; 96:751-4.

348.Annual Report of the Registrar General for Scotland, 1968 and 1979. Edinburgh, Her Majesty's Stationery Office.

349.Draep N, Smith H: Applied regression analysis. 2nd

ed. New York: John Wiley and Sons, 1981.

350.Armitage P: Statistical methods in medical research. Oxford: Blackwell Scientific Publications, chapter 9 and 12, 1971.

350.Annual Report of the Registrar General for Scotland 1985. Edinburgh, Her Majesty's Stationery Office.

351.Lilienfeld AM: Foundation of Epidemiology. New York: Oxford University Press. Chapter 5, 1976.

352.Yate PO: A change in the pattern of cerebrovascular disease. Lancet 1964; 1:65-69.

353.Israel RA, Klebba AJ: A preliminary report on the effect of eighth revision ICDA on cause of death statistics. Am J Public Health 1969; 59:1651-1660.

354.Florey CDV, Senter MG, Acheson RM: A study of the validity of the diagnosis of stroke in mortality data. I. Certificate analysis. Yale J Biol Med 1967; 40:148-163.

355.Peodoe HT. Stroke In: Miller DL, Farmer RD, eds., Epidemiology of Diseases, Blackwell Scientific Publication Chapter 9, 136-145, 1982.

356.Kurtzke JF: Epidemiology of cerebrovascular disease, cerebrovascular survey report for joint council subcommittee on cerebrovascular disease, National Institute of Neurological and Communicative Disorders and Stroke and National Heart and Lung Institute (revised), Jan 1976, Rochester, Minn, Whiting Press PP 213-242.

357.Moriyama I, Kruger DE, Stamler J: Cardiovascular diseases in the United States, Cambridge, Harvard University Press 1971.

358.Kuller et al.: Nationwide cerebrovascular mortality

study (IV): comparison of the different clinical types of cerebrovascular disease. Am J Epidemiol 1969; 90:567-578.

359.Manton KG, Baum HM: CVD mortality, 1968-1978: Observations and implications. Stroke 1984; 15:451-7.

360.Editorial: Cerebral Infarction and Myocardial Infarction : A similar aetiology? Lancet 1978; 1:1239-1246.

361.Annual Report of the Registrar General in Scotland 1977. Edinburgh, Her Majesty's Stationery Office.

362.Garraway WM, Whisnant JP, Drury I: The changing pattern of survival following stroke. Stroke 1983; 14:699-703.

363.Kannel WB, Gordon T, (eds):The Framingham Study -An Epidemiological Investigation of Cardiovascular Disease. Section 30: Some characteristics related to the incidence of cardiovascular disease and death: Framingham Study; 18-year follow-up. US Wash. DC. DHEW, Public Health Service. National Institute of Health, 1970.

364.Risk factors in stroke due to cerebral infarction, statement by the Council on Cerebrovascular Disease, American Heart Association. Stroke 1971; 2:423-428.

365.Haberman S, Capideo R, Rose FS: Epidemiological Aspects of Stroke. In: Greenhalgh RM. Rose FC eds. Progress in Stroke Research. Tunbridge Wells: Pitman Medical 3-14;1979.

366.Subcommittee on Risk Factors and Stroke of the Stroke Council. Risk Factors in Stroke. Special Report. Stroke 1984; 15:1105-11.

367.Kannel WB: Epidemiology of cerebrovascular disease.

In: Russell, RWR, ed. Cerebral arterial disease. Edinburgh Churchill Livingstone, 1976.

368.The General Household Survey, Office of Population Census and Surveys, Social Survey Division, London: Her Majesty's Stationery Office 1972-84.

369.General Household Survey, OPCS Monitor GHS 83/3 Issued 5 July 1983. Office of Population Census and Surveys. Information Branch, London: St. Catherines House, 10 Kingsway, London WC2B 5JP.

370.Lee PN, ed: Statistics of smoking in the United Kingdom. Tobacco Research Council, Research paper No. 1, 7th ed. London: Tobaco Research Council, 1976.

371.Florey CDV, Melia RJM, Darby SC: Changing mortality from ischaemic heart disease in Great Britain 1968-1976. Br Med J 1978; 1:635-677.

372.Veteran Administration Cooperative Study Group on Antihypertensive Agents. Effect of treatment on morbidity in hypertension: results in patients with diastolic blood pressure averaging 115 through 125 mmHg. JAMA 1967; 202:1143-52.

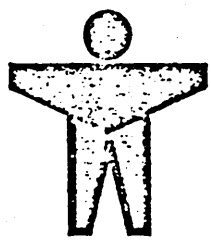
373.Hypertension Detection and Follow-up Programme Cooperative Group. Five year finding of the hypertension detection and follow-up programme. III. Reduction in stroke incidence among persons with high blood pressure. JAMA 1982; 247:633-8.

APPENDIX A

THE RENFREW AND PAISLEY QUESTIONNAIRE AND CODE SCHEDULE

CONFIDENTIAL

midspan health plan



conducted by the
Renfrewshire King Edward Memorial Trust,
Glasgow MMR Cardiorespiratory Screening Unit and the
Department of Epidemiology and Preventive Medicine
of the University of Glasgow.

(N=3059)
(100 secs)
13
VICDEM. RENF72V13
V1

For official use only

1.01	1.02	1.03	1.04	1.05	1.06	1.07

MMR reference number

Questionnaire and Health Record

PAISLEY.
(N = 13,112)
(300 secs to run)
VICDEM. PAIS73V8

This form may look a little long and difficult, but in fact it takes only a few minutes to answer.

Please answer all the questions in this health record and bring it with you when you come to the unit.
Write a tick (√) in the appropriate answer box.
If you cannot give an exact answer, give the best guess you can.

1 Surname (Mr., Mrs., Miss) .....
(BLOCK LETTERS)

If married or divorced woman—
Birth Surname (Maiden Name) .....

First Name(s) .....

Address .....

.....

Home Telephone Number .....

National Health Service Number .....
(if known)

Place of Birth .....

1.08	1.09	1.10	1.11	1.12	1.13	1.14

1.15	1.16	1.17	1.18	1.19	1.20

2 Sex ..... (M=1, F=2)

1.21 2

3 Are you

1 ☐ Married?
2 ☐ Widowed?
3 ☐ Single?
4 ☐ Other?

1.22 3

4 What is your date of birth?

Day of Month	Month	Year
.....	.....	.....

1.23	1.24	1.25	1.26	1.27	1.28

For official use only

5 What is your usual occupation?

If retired, please give last full-time occupation.
If you are a whole-time housewife, what is your husband's occupation?
Please describe as fully as possible.

.....

.....

.....

.....

1.29	1.30	1.31
	7	

6 Family Doctor. Dr.....

Address.....

.....

7 How much walking altogether do you do on the way to and from work on an average day? If you are a housewife, how much walking altogether do you do to and from the shops?

..... minutes

1.32	1.33	1.34
	8	

8 Do you usually bring up any phlegm from your chest first thing in the morning in the winter?

1 ☐ Yes **2** ☐ No

If 'No', go to question 11.

1.35 9

9 Do you bring up phlegm like this on most days for as much as three months in the winter each year?

1 ☐ Yes 2 ☐ No

1.36 10

10 In the past three years have you had a period of increased cough and phlegm lasting for three weeks or more?

1 ☐ Yes—1 period 3 ☐ No

2 ☐ Yes—2 or more periods

1.37 11

11 Do you get short of breath walking with people of your own age on level ground?

1 ☐ Yes 2 ☐ No

1.38 12

12 Does your chest sound wheezy or whistling on most days (or nights)?

1 ☐ Yes 2 ☐ No

1.39 13

13 Does the weather affect your breathing?

a 1 ☐ Yes 2 ☐ No

If 'No', go to question 14.

b If 'Yes':

1 Specify type of weather

.....

1.40 13a

2 Does it make your breathing

1 ☐ worse? 2 ☐ better?

1.41

For official use only

14 Do you smoke more than 5 cigarettes each day now?

a 1 ☐ Yes 2 ☐ No

b If 'Yes':

1 How many cigarettes do you usually smoke on an average day?

.....

2 At what age did you start smoking?

.....

3 Do you inhale?

1 ☐ Yes 2 ☐ No

1.42 1.43 1.44 1.45 1.46 1.47

15 If you do not smoke cigarettes now, did you ever smoke more than 5 a day regularly?

a 1 ☐ Yes 2 ☐ No, never

b If 'Yes':

1 At what age did you start smoking?

.....

2 At what age did you stop smoking?

.....

3 What is the most you ever smoked *per day* for as long as a year?

.....

1.48 1.49 1.50 1.51 1.52 1.53 1.54

16 **a** Have you ever had any pain or discomfort in your chest?

1 ☑ Yes 2 ☐ No (If 'No', go to question 17)

b Do you get this pain or discomfort when you walk uphill or hurry?

1 ☑ Yes 2 ☐ No

c Do you get it when you walk at an ordinary pace on the level?

1 ☐ Yes 2 ☑ No

d When you get any pain or discomfort in your chest what do you do?

1 ☐ Stop
2 ☑ Slow down
3 ☐ Continue at the same speed

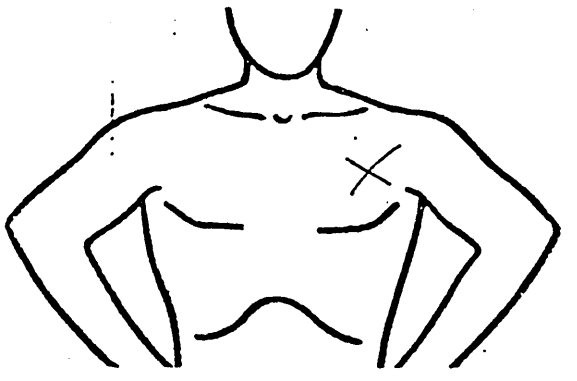
e Does it go away when you stand still?

1 ☑ Yes 2 ☐ No

f If 'Yes', how soon?

1 ☑ 10 minutes or less
2 ☐ More than 10 minutes

g Where do you get this pain or discomfort? Mark the place(s) with X on the diagram



1.55 1.56 1.57 1.58 1.59 1.60 1.61

17 Have you ever had a severe pain across the front of your chest lasting for half an hour or more?

1 ☐ Yes 2 ☑ No

1.62

For official use only

18 Are you, or have you ever been diabetic?

1 ☐ Yes
2 ☐ No
3 ☐ Do not know

1.63

19 Have you ever been in hospital?

a 1 ☐ Yes 2 ☐ No

If 'Yes' please give the following information for each time you went into hospital.

b	Year	Nature of illness or what was wrong?
1	.....	.....
2	.....	.....
3	.....	.....
4	.....	.....

(Continue on a separate sheet of paper if necessary.)

1.64 | 1.65 | 1.66 | 1.67 | 1.68

20 1 Have you ever had a stroke (shock)?

1 ☐ Yes 2 ☐ No

1.69

2 Have you ever, without warning:

a suddenly lost the power of an arm?
1 ☐ Yes 2 ☐ No — 1.70

b suddenly lost the power of a leg?
1 ☐ Yes 2 ☐ No — 1.71

c suddenly been unable to speak properly?
1 ☐ Yes 2 ☐ No — 1.72

d suddenly lost consciousness?
1 ☐ Yes 2 ☐ No — 1.73

3 Do you ever complain of headaches on one side of your head?
1 ☐ Yes 2 ☐ No — 1.74

21 Are you under the doctor for heart or blood pressure?

1 ☐ Yes 2 ☐ No

1.75

22 Do you suffer from, or have you ever suffered from:

a Asthma?
1 ☐ Yes 2 ☐ No — 1.76

b Hayfever?
1 ☐ Yes 2 ☐ No — 1.77

1.78 | 1.79

I understand that everything which could identify me will be treated as strictly confidential.

I do not object to any of my hospital records being looked at by members of the team to help them in the survey.

I wish / I do not wish the results of my examination to be sent to my family doctor.

1.80

Signature ....

Thank you for your help

For official use only

Name .....

M.M.R. reference number

Date .....

2.01	2.02	2.03	2.04	2.05	2.06	2.07

2.08	2.09	2.10	2.11	2.12	2.13
4	3	4	4	4	7

BLOOD PRESSURE

1 Systolic .....

2 Diastolic .....

Blood Pressure Observer

2.14	2.15	2.16
	4 6	

2.17	2.18	2.19
	4 7	

2.20	2.21
4	7

CHEST X-RAY

2.22	2.23
2	9

HISTORY

2.24
5 0

TINE TEST

Self reading

Observer reading

Tine tester

Tine Test Observer

2.25
5

2.26
5

(1 – 5)

2.27	2.28
5	

2.29	2.30
5	

SPUTUM

Direct

Culture

2.31
5 5

2.32
5 5

BLOOD

Serum cholesterol

Sugar

Blood sampler

~~Time of sample~~

HEART WIDTH

THORACIC WIDTH

2.33	2.34	2.35
	5	

2.36	2.37	2.38
	5 5	

2.39	2.40
5	9

2.41	2.42	2.43	2.44
	6 0		

ANGINA

2.45
5 9

ANTHROPOMETRY

Height (without shoes) cms.

Weight (indoor clothing) kilos.

Observer

2.46	2.47	2.48
	5 2	

2.49	2.50	2.51	2.52
	5 2		

2.53	2.54
5	3

E.C.G. i ..... ii ..... iii .....

iv ..... v ..... vi .....

vii ..... viii ..... ix .....

E.C.G. Summary

Operator

Coder

Adjudicator

i 2.55	2.56	ii 2.57	2.58	iii 2.59	2.60
iv 2.61	2.62	v 2.63	2.64	vi 2.65	2.66
vii 2.67	2.68	viii 2.69	2.70	ix 2.71	2.72

2.73
65

2.74	2.75
66	
2.76	2.77
67	
2.78	2.79
68	

M.M.R. reference number

2.80
2

3.01	3.02	3.03	3.04	3.05	3.06	3.07

RESPIRATORY FUNCTION

F.E.V. 1.0

F.V.C.

Respiratory Function Tester

3.08	3.09	3.10
	69	
3.11	3.12	3.13
	70	
3.14	3.15	
71		

CATEGORY

3.16	3.17
72	
3.18	3.19
3.20	3.21
3.22	3.23

Interviewer or questionnaire checker

Coder

Checker

Secondary Screening

Date

Systolic

Diastolic

Observer

Serum Cholesterol

Sugar

Blood sampler

Time of sample

3.24	3.25	3.26	3.27	3.28	3.29
73		74		75	

3.30	3.31	3.32
	76	

3.33	3.34	3.35
	77	

3.36	3.37

3.38	3.39	3.40
	78	

3.41	3.42	3.43
	79	

3.44	3.45

3.46	3.47	3.48	3.49
	80		

E.C.G. i ..... ii ..... iii .....

iv ..... v ..... vi .....

vii ..... viii ..... ix .....

i 3.50	3.51	ii 3.52	3.53	iii 3.54	3.55
iv 3.56	3.57	v 3.58	3.59	vi 3.60	3.61
vii 3.62	3.63	viii 3.64	3.65	ix 3.66	3.67

E.C.G. Summary

3.68
81

Operator

3.69	3.70

Coder

3.71	3.72

Adjudicator

3.73	3.74

3.75	3.76	3.77	3.78	3.79
82	83	84		

(Pairing only)

3.80
3

M.M.R. reference number

4.01	4.02	4.03	4.04	4.05	4.06	4.07

Contacts

Number of Contacts .....

4.08	4.09

Contacts X-rayed .....

4.10	4.11

Positive X-rays .....

4.12	4.13

Contacts Tine Tested .....

4.14	4.15

Positive Tine Tests .....

4.16	4.17

Contacts sputa .....

4.18	4.19

direct .....

4.20	4.21

culture .....

4.22	4.23

FINAL CATEGORY

4.24	4.25
82	

C.O.D.

4.26	4.27	4.28	4.29
	83		//

Group C.O.D.

4.30
84

4.31	4.32	4.33

Survey No. DD, MD, YD

Date of Decl 4:36 - 4:41

4.34	4.35

Serial Obs. No. Risk Score 4:42 - 4·44 (F3.1)

Carboxyhaemoglobin 4:53 - 4·55 (F3.1) CRSxYR

85

4.36	4.37	4.38	4.39	4.40	4.41	4.42

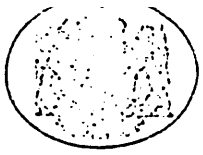
CANCER INCIDENCE SITE 4·64 -> 4·67

4.43	4.44	4.45	4.46	4.47	4.48	4.49

Date Treatment Commenced 4·68 -> 4·73

4.80
4

388 86, 87, 88



CARD 5

Columns

1-7 M.M.R Survey No.

8-20 Smoking habits of spouse as per columns 1:42 – 1:54

8 Do you smoke more than 5 cigarettes each day now 1 = Yes 2 = No V89

If yes

9,10 How many cigarettes do you usually smoke on an average day V90

11,12 At what age did you start smoking V91

13 Do you inhale 1 = Yes 2 = No V92

14 If You do not smoke cigarettes now, did you ever smoke more than 5 a day regularly 1 = Yes 2 = No never V93

If yes

15,16 At what age did you start smoking V94

17,18 At what age did you stop smoking V95

19,20 What is the most you ever smoked per day for as long as a year V96

Secondary causes of death ICD (8)

21-24
25-28
29-32
} Remaining causes of death

" Morbidity (hospital)

33-38 Date

39-42 Cause

43-48 Date

49-52 Cause

53-58 Date

59-62 Cause

80 5 (card number)

KENFREW

2. CARD 1 : QUESTIONNAIRE CODES

Question No.	Item	Code	Box
	M.M.R. RECORD NO.	X-Ray Ref. Number	1.01 - 1.07 (7)
1.	NATIONAL HEALTH SERVICE NO.	Standard 13-Digit Number	1.08 - 1.20 (13)
2.	SEX		
	Male	1	
	Female	2	1.21 (1)
3.	MARITAL STATUS	Pre-coded	1.22 (1)
4.	DATE OF BIRTH		
	Day	01 - 31	1.23 - 1.24 (2)
	Month	01 - 12	1.25 - 1.26 (2)
	Year	Last two digits	1.27 - 1.28 (2)
5.	OCCUPATION	From Registrar-General's Classification	1.29 - 1.31 (3)
7.	EXERCISE ON WAY TO WORK	Code No. of minutes	1.32 - 1.34 (3)
	BRONCHITIS		
8.	PHLEGM	Pre-coded	1.35 (1)
9.	PERSISTENT PHLEGM	Pre-coded	1.36 (1)
10.	PHLEGM INFECTION	Pre-coded	1.37 (1)
11.	DYSPNOEA	Pre-coded	1.38 (1)
12.	HYPERSECRETION	Pre-coded	1.39 (1)
13(a)	SUSCEPTIBILITY TO ATMOSPHERIC POLLUTION	No effect Code 2	1.40 (1)
13(b1)	CODE 3: Fog, Mist, Smog CODE 4: Cold, Cool damp, Frost, Winter, wind CODE 5: Rain, Damp, Humid	If yes, look at 13b and code 3-7 as appropriate	(1.40)

CARD 1

Question No.	Item	Code	Box	
13(b1) (Contd.)	CODE 6 Sun Exceptionally, or very warm or hot Warm Summer Warm Windless Humidity Dry Summer Heat Airless or Sultry Clammy, heavy or close.		(1.40)	
	CODE 7 Other Sunny and showery Before rain All weather except sunny days Climatic position Where more than one condition code according to priority - e.g., Code 3 preferred to Code 4, etc.	If yes, look at 13b and code 3-7 as appropriate	(1.40)	
13(b2)	Effect on breathing	Pre-coded	1.41	(1)
	CIGARETTES			
14(a)	SMOKER	Pre-coded	1.42	(1) ✓
14(b1)	NUMBER	Code actual number smoked (99 = 100 or more). If range use mean 01 - 99	1.43 - 1.44	(2) ✓
14(b2)	AGE WHEN SMOKING BEGAN	Code age given. (For ages up to nine years, code 01, 02, etc.)	1.45 - 1.46	(2) ✓
14(b3)	INHALATION	Pre-coded	1.47	(1) ✓
	EX-SMOKERS			
15(a)	SMOKING	Pre-coded	1.48	(1) ✓
15(b1)	AGE WHEN SMOKING BEGAN	Code age given. (For ages up to nine years, code 01, 02, etc.)	1.49 - 1.50	(2) ✓
15(b2)	AGE WHEN SMOKING STOPPED	Code age given	1.51 - 1.52	(2) ✓
15(b3)	MAXIMUM SMOKED	Code as for 14(b1)	1.53 - 1.54	(2) ✓

CARD 1

Question No.	Item	Code	Box	
	ISCHAEMIC HEART DISEASE			
16(a)	GENERAL CHEST PAIN	Pre-coded	1.55	(1)
16(b)	PAIN ON MARKED EXERTION	Pre-coded	1.56	(1)
16(c)	PAIN ON EXERTION	Pre-coded	1.57	(1)
16(d)	ACTION ON PAIN	Pre-coded	1.58	(1)
16(e)	EFFECT ON PAIN	Pre-coded	1.59	(1)
16(f)	DURATION OF PAIN	Pre-coded	1.60	(1)
16(g)	LOCATION OF PAIN:			
	Sternum (upper/middle third)	1	1.61	(1)
	Sternum (lower third)	2	(1.61)	
	Left chest and left arm	3	(1.61)	
	Left chest only	4	(1.61)	
	Left arm only	5	(1.61)	
	Other	6	(1.61)	
	(Priority in order)			
17	SEVERE CHEST PAIN	Pre-coded	1.62	(1)
	DIABETES			
18	DIABETES - EXISTENCE OF	Pre-coded	1.63	(1)
	HOSPITAL HISTORY			
19(a)	HOSPITAL ADMISSION	Pre-coded	1.64	(1)
19(b)	NUMBER OF ADMISSIONS			
	Enter total number of admissions n_i (9 = 9 or more) opposite appropriate heading, as follows:-			
	NUMBER OF ADMISSIONS FOR BRONCHITIS, PNEUMONIA, AND OTHER CHEST DISEASES, INCLUDING INFLUENZA.	n_1	1.65	(1)
	NUMBER OF ADMISSIONS FOR HEART DISEASE	n_2	1.66	(1)
	NUMBER OF ADMISSIONS FOR PEPTIC (GASTRIC OR DUODENAL) ULCER	n_3	1.67	(1)
	NUMBER OF ADMISSIONS FOR RHEUMATIC FEVER, CHOREA, AND OTHER CONDITIONS, INCLUDING INJURIES	n_4	1.68	(1)

CARD 1

Question No.	Item	Code	Box	
	STROKE			
20/1	STROKE - EXISTENCE OF	Pre-coded	1.69	(1)
	LOSS OF POWER			
20/2(a)	Arm	Pre-coded	1.70	(1)
(b)	Leg	Pre-coded	1.71	(1)
(c)	Speech	Pre-coded	1.72	(1)
(d)	Consciousness	Pre-coded	1.73	(1)
20/3	HEADACHES	Pre-coded	1.74	(1)
	HEART OR BLOOD PRESSURE			
21	DOCTOR CONSULTATION	Pre-coded	1.75	(1)
	ASTHMA AND HAY-FEVER			
22(a)	ASTHMA - EXISTENCE OF	Pre-coded	1.76	(1)
22(b)	HAY-FEVER - EXISTENCE OF	Pre-coded	1.77	(1)
	No. of years of residence at stated address.	Act. No. of years (rounded up)	1.78 - 1.79	(2)
	CARD SERIAL NUMBER PRINTED 1	Pre-printed	1.80	(1)

3. CARD 2 : HEALTH CHECK CODES

Item	Code	Box
OBJECTIVE DATA		
M.M.R. RECORD NO.	As on Questionnaire 1.01 - 1.07	2.01 - 2.07 (7)
DATE		
Code day	01 - 31	2.08 - 2.09 (2)
Code month	01 - 12	2.10 - 2.11 (2)
Code year	Last two digits	2.12 - 2.13 (2)
BLOOD PRESSURE		
SYSTOLIC	Code actual reading	2.14 - 2.16 (3)
DIASTOLIC	Code actual reading	2.17 - 2.19 (3)
BLOOD PRESSURE OBSERVER	Observer's code number	2.20 - 2.21 (2)
CHEST X-RAY		
STANDARD M.M.R. CLASSIFICATION	01 - 31	2.22 - 2.23 (2)
31. No abnormality	31	(2.22 - 2.23)
01. Abnormalities of the Bony Thorax and Soft Tissues - congenital to include abnormalities of Ribs Spine Sternum Bifid Ribs or Depressed Sternum e.g. depressed sternum spina bifida wedge vertebrae.	01	(2.22 - 2.23)
02. Abnormalities of the Bony Thorax and Soft Tissues - acquired e.g. fractures malformation due to polio osteo-chondritis of the dorsal spine tuberculosis Paget's disease actinomycosis Fracture of rib, Scoliosis, Kyphoscoliosis.	02	(2.22 - 2.23)

CARD 2

Item	Code	Box
03. Tumours of the Bony Thorax - primary and secondary: e.g. osteo-chondromata chondromata fibromata sacromata reticulosis	03	(2.22 - 2.23)
04. Congenital malformations of the lungs: to include lobar malformations accessory lobes azygos lobe agenesis ectopic segments haemartoma haemangiomas arterio-venous aneurysms	04	(2.22 - 2.23)
05. Bacterial and virus infection of the lungs: to include lung abscess pneumonitis pneumonia to exclude infections secondary to malignancy and all aspiration chemical pneumonias.	05	(2.22 - 2.23)
06. Other infections of the lungs: to include hydatid disease syphilis fungus infection histoplasmosis	06	(2.22 - 2.23)
07. Bronchiectasis	07	(2.22 - 2.23)
08. Honeycomb lung	08	(2.22 - 2.23)
09. Emphysema to include hypertrophic bullous obstructive interstitial	09	(2.22 - 2.23)
10. Pulmonary fibrosis - non tuberculous to include asthma bronchitis post-infective fibrosis secondary to pneumonitis (suppurative pneumonias) and chemical pneumonias, oil achalasia fumes,etc. Fibrosis and bronchial thickening.	10	(2.22 - 2.23)

CARD 2

	Item	Code	Box
	11. Pneumoconiosis Asbestosis Inhalation fibrosis	11	(2.22 - 2.23)
	12. Spontaneous pneumothorax	12	(2.22 - 2.23)
	13. Benign tumours of the lungs and mediastinum: to include pulmonary fibromas endothiliomas neurofibromas substernal thyroid all mediastinal cysts exastosis of the rib	13	(2.22 - 2.23)
	14. Carcinoma or other malignant disease of the lung and mediastinum. (neoplasm)	14	(2.22 - 2.23)
	15. Metastases in the lung and mediastinum	15	(2.22 - 2.23)
	16. Enlarged mediastinal and bronchial glands - non tuberculous to include reticulosis glandular fever and other rare causes except Hodgkin's disease enlarged roots hilar adenitis lymph adenitis enlarged cervical glands	16	(2.22 - 2.23)
	17. Sarcoidosis and collagenous diseases to include glandular and pulmonary stages.	17	(2.22 - 2.23)
	18. Pleural thickening or calcification (non tuberculous) to include sequelae of empyema (adhesions) haemothorax etc. pleurisy calcification of the pleura pleural effusion.	18	(2.22 - 2.23)
	19. Abnormalities of the diaphragm and oesophagus - congenital and acquired: to include all types of hernia cardiospasm oesophageal strictures diverticula eventration of diaphragm	19	(2.22 - 2.23)

CARD 2

Item	Code	Box
20. Congenital abnormalities of heart and vessels: to include abnormal venous drainage dextro-cardia right-sided aorta, etc. Congenital malformation of heart Unfolded aorta Cardiac enlargement	20	(2.22 - 2.23)
21. Acquired abnormalities of heart and vessels: to include aneurysms haemosiderosis, etc. acquired mitral stenosis hypertension restricted pericardium	21	(2.22 - 2.23)
22. Miscellaneous: to include empyema foreign body in lung etc. pneumonectomy embolism	22	(2.22 - 2.23)
23. Pneumoconiosis with tuberculosis	23	(2.22 - 2.23)
24. Pulmonary tuberculosis. Active	24	(2.22 - 2.23)
25. Pulmonary tuberculosis. Of doubtful activity but requiring observation.	25	(2.22 - 2.23)
26. Tuberculous pleural effusion without demonstrable pulmonary lesion (tuberculous pleurisy)	26	(2.22 - 2.23)
27. Tuberculosis - inactive and healed - primary calcified glands healed primary calcified pleural plaque calcified arch of aorta	27	(2.22 - 2.23)
28. Tuberculosis - inactive and healed - post primary inactive P.T. tuberculoma	28	(2.22 - 2.23)
29. For Chest Clinic use	29	(2.22 - 2.23)
30. Not yet diagnosed.	30	(2.22 - 2.23)

CARD 2

Item	Code	Box
HISTORY from M.M.R. Card		
	(Code first disease given)	2.24 (1)
Chest disease including T.B.	1	(2.24)
Coronary disease	2	(2.24)
Heart disease other than coronary	3	(2.24)
Hypertension	4	(2.24)
Peripheral vascular disease	5	(2.24)
Diabetes	6	(2.24)
Other	7	(2.24)
TINE TEST		
SELF-READING	1 - 6	2.25 (1)
Nothing to see	1	(2.25)
Very pale reaction	2	(2.25)
1 - 4 raised dots	3	(2.25)
4 raised red dots running into each other	4	(2.25)
A raised red lump ¼ inch or more across	5	(2.25)
Other	6	(2.25)
OBSERVER READING Code as above	1 - 6	2.26 (1)
TINE TESTER	Tester's code number	2.27 - 2.28 (2)
TINE TEST OBSERVER	Observer's code number	2.29 - 2.30 (2)
SPUTUM		
DIRECT		
Negative	1	2.31 (1)
Positive	2	(2.31)
CULTURE		
Negative	1	2.32 (1)
Positive	2	(2.32)
BLOOD		
SERUM CHOLESTEROL in mgm. per cent.	Code actual value	2.33 - 2.35 (3)
SUGAR	Code actual value	2.36 - 2.38 (3)
BLOOD SAMPLER	Sampler's code number	2.39 - 2.40 (2)
HEART MEASUREMENT G		2.41 - 2.42 (2)
H		2.43 - 2.44 (2)

CARD 2

	Item	Code	Box	
	ANGINA			
	GRADE 4 No to 16(a)	4	2.45	(1)
	GRADE 1 Yes to 16(a) and 16(b) and No to 16(c), and Stop or Slow down to 16(d) and Yes to 16(e), and 10 minutes or less to 16(f), and 'X' on sternum or left anterior chest + left arm	1	(2.45)	
	GRADE 2 As grade 1, but Yes to 16(c)	2	(2.45)	
	GRADE 3 Yes to 16(a) + any other answers	3	(2.45)	
	HEIGHT	Code cms.	2.46 - 2.48	(3)
	WEIGHT	Code kilos	2.49 - 2.52	(4)
	OBSERVER	Observer's code number	2.53 - 2.54	(2)
	E.C.G.			
	MINNESOTA CODE	Code actual reading for each number in the corresponding two boxes	2.55 - 2.72	(18)
	E.C.G. SUMMARY			
	a. 1:1, 1:2, 7:1	1	2.73	(1)
	b. 1:3, 4:1, 4:2, 4:3, 5:1, 5:2, 5:3	2	(2.73)	
	c. All other codes except those in code 1 and code 2	3	(2.73)	
	d. If (i) = 1.0	9	(2.73)	
	OPERATOR	Operator's code number	2.74 - 2.75	(2)
	CODER	Coder's code number	2.76 - 2.77	(2)
	ADJUDICATOR	Adjudicator's code number	2.78 - 2.79	(2)
	CARD SERIAL NO. PRINTED 2	Pre-printed	2.80	(1)

4. CARD 3 : HEALTH CHECK CODES (Contd.)

Item	Code	Box
M.M.R. RECORD NO.	As in Questionnaire Boxes 1.01 - 1.07	3.01 - 3.07 (7)
RESPIRATORY FUNCTION		
F.E.V. 1	Code actual figure	3.08 - 3.10 (3)
F.V.C.	Code actual figure	3.11 - 3.13 (3)
RESPIRATORY FUNCTION TESTER	Tester's code number	3.14 - 3.15 (2)
CATEGORY		
If only screened once - enter code in box 3.17. If recalled for secondary screening enter 9 in box 3.17 and code in box 4.25. 9 in box 3.17 will indicate a recall for secondary screening. 9 in box 4.25 will indicate that the person concerned has died between primary and secondary screening.		
A	01	3.16 - 3.17 (2)
B_1	02	(3.16 - 3.17)
B_2	03	(3.16 - 3.17)
B_3	04	(3.16 - 3.17)
Who treat	05	(3.16 - 3.17)
Who control	06	(3.16 - 3.17)
C	07	(3.16 - 3.17)
D	08	(3.16 - 3.17)
NOTE: Any person who does not fit into the above categories will be left blank. 0 will not be used.		(3.16 - 3.17)
INTERVIEWER OR QUESTIONNAIRE CHECKER	Checker's code number	3.18 - 3.19 (2)
CODER	Coder's code	3.20 - 3.21 (2)
CHECKER	Checker's code number	3.22 - 3.23 (2)

CARD 3

Item	Code	Box	
SECONDARY SCREENING			
DATE.			
Code day	01 - 31	3.24 - 3.25	(2)
Code month	01 - 12	3.26 - 3.27	(2)
Code year	Last two digits	3.28 - 3.29	(2)
BLOOD PRESSURE			
SYSTOLIC	Code actual reading	3.30 - 3.32	(3)
DIASTOLIC	Code actual reading	3.33 - 3.35	(3)
BLOOD PRESSURE OBSERVER	Observer's code number	3.36 - 3.37	(2)
BLOOD			
SERUM CHOLESTEROL in mgm. per cent.	Code actual value	3.38 - 3.40	(3)
SUGAR	Code actual value	3.41 - 3.43	(3)
BLOOD SAMPLER	Sampler's code number	3.44 - 3.45	(2)
TIME OF SAMPLE	Code hour and minute using 24-hour clock	3.46 - 3.49	(4)
E.C.G.			
MINNESOTA CODE	Code actual reading for each number in the corresponding two boxes.	3.50 - 3.67	(18)
E.C.G. SUMMARY			
a. 1:1, 1:2, 7:1	1	3.68	(1)
b. 1:3, 4:1, 4:2, 4:3, 5:1, 5:2, 5:3	2	(3.68)	
c. All other codes except those in code 1 and code 2	3	(3.68)	
d. If(i)= 1.0	9	(3.68)	
OPERATOR	Operator's code number	3.69 - 3.70	(2)

CARD 3

	Item	Code	Box	
	CODER	Coder's code number	3.71 - 3.72	(2)
	ADJUDICATOR	Adjudicator's code number	3.73 - 3.74	(2)
	Area of Residence	1 or 2	3.75	(1)
	SPARE		3.76 - 3.79	(4)
	CARD SERIAL NUMBER PRINTED 3	Pre-printed	3.80	(1)

5. CARD 4 : HEALTH CHECK CODES (Contd.)

Item	Code	Box
M.M.R. RECORD NO.	Code Number in questionnaire boxes 1.01 - 1.07	4.01 - 4.07 (7)
CONTACTS		
NUMBER OF CONTACTS	Code number	4.08 - 4.09 (2)
CONTACTS X-RAYED	Code number	4.10 - 4.11 (2)
POSITIVE X-RAYS	Code number	4.12 - 4.13 (2)
CONTACTS TINE-TESTED	Code number	4.14 - 4.15 (2)
POSITIVE TINE TESTS	Code number	4.16 - 4.17 (2)
CONTACTS		
SPUTA	Code number	4.18 - 4.19 (2)
DIRECT	Code number	4.20 - 4.21 (2)
CULTURE	Code number	4.22 - 4.23 (2)
FINAL CATEGORY		
If only screened once - enter in box 3.17. If recalled for secondary screening enter 9 in box 3.17 and code in box 4.25. 9 in box 3.17 will indicate a recall for secondary screening. 9 in box 4.25 will indicate that the person concerned has died between primary and secondary screening.		4.24 - 4.25 (2)
A	01	(4.24 - 25)
B_1	02	(4.24 - 25)
B_2	03	(4.24 - 25)
B_3	04	(4.24 - 25)
Who treat	05	(4.24 - 25)
Who control	06	(4.24 - 25)
C	07	(4.24 - 25)
D	08	(4.24 - 25)
NOTE: Any person who does not fit into the above categories will be left blank. 0 will not be used.		

CARD 4

Item	Code	Box	
DECEASED			
C.O.D. This is a three figure number, but in some cases may be subdivided, e.g., 286.2. Therefore the first three boxes are the three figure numbers, and the fourth box is the sub-division.	Use International Classification of Diseases. Eighth Revision	4.26 - 4.29	(4)
GROUP CLASSIFICATION OF DECEASED		4.30	(1)
Coronary Heart Disease ± Hypertension	2	(4.30)	
Cerebral Vascular Disease ± Hypertension	3	(4.30)	
Other Vascular Disease	4	(4.30)	
Lung Cancer	5	(4.30)	
Chronic Bronchitis	6	(4.30)	
Respiratory Infarctions	7	(4.30)	
Other	8	(4.30)	
Unknown	9	(4.30)	
SURVEY NUMBER		4.31 - 4.33	(3)
SERIAL OBSERVATION NO.		4.34 - 4.35	(2)
DATE OF DEATH	CODE DAY	4.36 - 4.37	(2)
	CODE MONTH	4.38 - 4.39	(2)
RISK SCORE	CODE YEAR	4.40 - 4.41	(2)
	CODE ACTUAL VALUE to 1 decimal place	4.42 - 4.44	(3)
*Na/CO		4.45 - 4.47	(3)
*K		4.48 - 4.49	(2)
02		4.50 - 4.52	(3)
Hb. (mark in RED on front questionnaire results of 10 and under)		4.53 - 4.55	(3)
CO		4.56 - 4.58	(3)
*Pb		4.59 - 4.61	(3)
*Treatment		4.62 - 4.63	(2)
		4.64 - 4.78	(15)
SPARE			
NEUROSIS	Negative = 1 Positive = 2	4.79	(1)
CARD SERIAL NO. PRINTED 4	PRE-PRINTED	4.80	(1)

APPENDIX B

FOLLOW-UP QUESTIONNAIRE AND REMINDER LETTERS

University of Glasgow
Department of Community Medicine
2, Lilybank Gardens,
Glasgow G12 8QQ.

MIDSPAN HEALTH PLAN

FOLLOW-UP SURVEY CONDUCTED BY THE DEPARTMENT OF COMMUNITY MEDICINE, UNIVERSITY OF GLASGOW

Dear

You may remember that about 10-14 years ago, you participated in a research project (called MIDSPAN) in which you completed a questionnaire and had a medical check-up. We wish to follow-up this study to find out more about the health of these people now. We hope you will be able to help us in this research by answering all the following questions and returning the questionnaire in the prepaid envelope.

All information will be used only by the doctors engaged in this survey and will not be available to any other person.

Yours sincerely,

A.J. Hedley.
Professor of Public Health.

Please could you check these details, ticking the left hand column if correct, or writing corrections in the right hand column if incorrect.

TICK BOX IF CORRECT	OR	ENTER CORRECTIONS HERE
[	]	.....
		.....
		.....
		.....
[	]	.....
[	]	.....
		.....
		.....
		.....
[	]	.....

Please tick [✓] the appropriate box or answer in the space provided. If you can not give the exact answer, please give the best guess you can.

The first few questions are about diabetes. We are interested to find out how many people who were known not to have diabetes at the time of the earlier survey have since developed it

1. Did a doctor ever tell you that you had diabetes (that is Sugar Diabetes or sugar in your urine)?
   [ ] YES [ ] NO [ ] DON'T KNOW.

   When ? .....

If you have diabetes, please answer questions 2-4.
If not, then go to question 5.

---

2. Have you ever been admitted to hospital for diabetes?
   [ ] YES [ ] NO

   When ?..... For how long ?.....

   At which hospital? .....

---

3. Have you ever had any treatment for diabetes?
   [ ] NO [ ] YES If yes, which type of treatment? (Insulin injections []
   (Tablets []
   (Others .....
   (specify)

If you have never been treated for diabetes, go to question 5.

---

4. In which year were you first treated for diabetes ? 19 [_ _]

   Do you still receive treatment for diabetes? [ ]YES [ ] NO

   If not, in which year did you stop being treated? 19 [_ _]

---

5. What is your weight now? [ ] Stones [ ] pounds
   (Indoor clothes and without shoes)

---

6. What is your height now (without shoes)? [ ] Feet [ ] Inches

---

I DO NOT OBJECT TO MY MEDICAL RECORDS BEING LOOKED AT BY A MEMBER OF THE HEALTH TEAM TO HELP THEM IN THE SURVEY.

SIGNATURE : .....

YOU HAVE COMPLETED THE QUESTIONNAIRE. THANK YOU VERY MUCH FOR YOUR HELP. PLEASE RETURN IT IN THE PREPAID ENVELOPE

UNIVERSITY OF GLASGOW

Department of Community Medicine

2 Lilybank Gardens
Glasgow G12 8QQ
Telephone: 041-339 8855
Direct Dialling: 041-330 5013
Telex: 777070 UNIGLA

enry Mechan Chair of Public Health & Head of Department
rofessor A J Hedley MD FRCP FFCM

RBJ/17.

January, 1988.

Dear

MIDSPAN HEALTH PLAN

A few weeks ago, we wrote to you hoping that you would be able to help us with a research project by completing and returning a questionnaire. So far we have not received a reply from you. In case you did not receive our original request we enclose a further copy of the original letter and questionnaire and hope that you will be able to help us.

With best wishes.

Yours sincerely,

A.J. Hedley,
Professor of Public Health.

UNIVERSITY OF GLASGOW

Department of Community Medicine

2 Lilybank Gardens
Glasgow G12 8QQ
Telephone: 041-339 8855
Direct Dialling: 041-330 5013
Telex: 777070 UNIGLA

Henry Mechan Chair of Public Health & Head of Department
Professor A J Hedley MD FRCP FFCM

RBJ/17.

March, 1988.

Dear

ARGYLL & CLYDE HEALTH BOARD
MIDSPAN HEALTH PLAN

A few weeks ago, we wrote to you hoping that you would be able to help us with a follow-up enquiry to the "Midspan" health examination of the 1970's. So far we have not received a completed questionnaire from you. In case you did not receive our original request we enclose a further copy of the original letter and questionnaire. We hope that you will be able to help us with this health survey.

With best wishes.

Yours sincerely,

A.J. Hedley,
Professor of Public Health.

UNIVERSITY OF GLASGOW

Department of Community Medicine

2 Lilybank Gardens
Glasgow G12 8QQ
Telephone: 041-339 8855
Direct Dialling: 041-330 5013
Telex: 777070 UNIGLA

enry Mechan Chair of Public Health & Head of Department
rofessor A J Hedley MD FRCP FFCM

RBJ/17.

Dear Dr.

ARGYLL & CLYDE HEALTH BOARD
FOLLOW-UP TO MIDSPAN SURVEY

In the mid 1970's, this department, in collaboration with others, carried out a survey of all 45-65 year olds in Renfrew and Paisley. The project went under the name MIDSPAN. The survey population has been followed up in the subsequent period by notification of deaths from the central registry.

Last October, we applied to the GP Sub-Committee of Argyll & Clyde Health Board for permission to send postal questionnaires to a sample of patients; the Committee agreed to our request. Our aim is to assess the predictive value of a random blood glucose measurement for the subsequent development of diabetes.

We have now completed our patient survey and we wish to check the accuracy of data obtained from the patient questionnaires. A summary of replies from your patients is enclosed. Would you be able to confirm that the details we have been given are correct and add amendments where necessary? All information will, of course, be handled with the utmost confidentiality.

If you wish to receive a summary of the results of this study when completed, please tick the relevant box on the attached form.

We enclose a prepaid envelope.

Thank you very much for your help in anticipation.

Yours sincerely,

A.J. Hedley,
Professor.

UNIVERSITY OF GLASGOW

Department of Community Medicine

2 Lilybank Gardens
Glasgow G12 8QQ
Telephone: 041-339 8855
Direct Dialling: 041-330 5013
Telex: 777070 UNIGLA

Henry Mechan Chair of Public Health & Head of Department
Professor A J Hedley MD FRCP FFCM

RBJ/27.

Dear Dr.

Argyll & Clyde Health Board
Follow-up to MIDSPAN survey

We wrote to you recently to seek your help with this follow-up study of subjects at-risk of developing diabetes. A copy of our original letter is enclosed. As we have not yet heard from you, I hope you will not mind if we approach you once more with this reminder. We have had an excellent response from our general practitioner colleagues but would, of course, hope to make our sample complete.

I would be very grateful if you could find time to complete the attached enquiry form and return it to us.

Thank you for your help.

Yours sincerely,

A.J. Hedley.

APPENDIX C

THE MIDSPAN PUBLICATIONS AND PRESENTATIONS

1964-1988

APPENDIX C

THE MIDSPAN PUBLICATIONS AND PRESENTATIONS 1964-1988

1.Hawthorne VM: Mass radiography in an ecological approach to respiratory disease. Scot Med J 1964; 9:115.

2.Hawthorne VM: An epidemiological method to improve tuberculosis control. Scot Med J 1969; 14:222.

3.Hawthorne VM, Gillis CR, Lorimer AR, Calvert FR, and Walker TJ: Blood pressure in a Scottish island community. BMJ 1969; 2:651.

4.Hawthorne VM:The health check in practice. The Glasgow post-graduate Medical Board, Educare, Hemel Hemstead, 1970.

5.Hawthorne VM, Gillis CR, and Lorimer AR: Multiphasic screening findings in volunteers examined at the C.H.A. Health Exhabition in Glasgow. The Medical Officer. 1970; CXXIV:253.

6.Hawthorne VM: Population screening as a personalized method of health education. Soc Sci & Med 1970; 3:653.

7.Lorimer AR, Hawthorne VM, Morgan AG: Plasma lipid values and prevalence of hyperlipoproteinaemia in the west of Scotland. Ann Biol Clin 1973; 31:149.

8.Hawthorne VM: Prevalence of cardiovascular disease in a Scottish Burgh. Tubercle, B.T.T.A. Review. 1973; 3:2, 24.

9.Hawthorne VM: A personalized approach to health education. The Journal of the Institute of Health Education, 1970; 8:4, 112.

10.Hawthorne VM, Gillis CR, and Maclean DS. Monitoring Health in Scotland. Int J Epid. 1972; 1:4, 369.

11.Calvert FR, Hawthorne VM, Mann PG, and Sandys GH: Bacteriuria in a Scottish island community. A comparison of chemical and cultural tests for bacteriuria applied in renote surroundings. J Hyg Camb 1972; 70:105.

12.Greaves DA, Hawthorne VM, Hilary McCartney, Murdoch RM: The collaborative study on smoking in Scotland: a preliminary report on prevalence rates and values in 10,000 subjects by occupational and general population groups. University of Glasgow Dept. of Epidemiology and Preventive Medicine, 1973.

13.Hawthorne VM, Greaves DA, Beevers DG: Blood pressure in a Scottish town. BMJ 1974; 3:600.

14.Padfield PL, Nelson CS, Beevers DG, (speaker), Hawthorne VM et al.: Hypertension and reninangiotension system in an unselected population. Hypertension -its nature and treatment. CIBA International Symposium, Malta. 1974; 19.

15.Hawthorne VM: Screening for disease. Lancet, 1975; 1:326.

16.Hawthorne VM, Greaves DA, and Beevers DG: Community studies of hypertension in Glasgow. In Epidemiology and Control Of Hypertension, Ed. Paul Oglesby. Medical books, Florida 1975; 537-551.

17.Beevers DG, Hawthorne VM, and Sinclair RG: The detection and management of hypertension in a Scottish urban community. In Proc. Pathophysiology and Management of Arterial Hypertension, Coopenhagen, Ed. L. Werki. 1975; 263.

18.Hawthorne VM: Mass health examination in Scotland.

International Symposium on preventive cardiology. The Irish Heart Foundation, Dublin. 1975.

19. Jubb JS, Lorimer AR, Hawthorne VM, Morgan HG, and Lawrie TDV. Lipoprotein levels in apparently healthy men and women in the west of Scotland. Brit Heart J 1976; XXXVIII:11, 1189.

20. Beevers DG, Campbell BC, Goldberg A, Moore MR, and Hawthorne VM: Blood cadmium in hypertensives and normotensives. Lancet, 1976; II:1222.

21. Hawthorne VM, Beevers DG, Gilmour H, Stewart, GM, and Watt H. Effectiveness of screening for hypertension in Scotland. Clin Sci and Mol Med 1976; 51:653.

22. Hawthorne VM. Screening for blood pressure in Scotland. Supplement to Annals of Academy of Medicine. Singapore. 1976; 5:3, 2.

23. Eshleman RF, Hawthorne VM. Normative structure and Health: A Socio-environmental adaptation model. Social Science and Medicine, 1976; 9:11, 665.

24. Hawthorne VM: Migration and stroke mortality in Great Britain. Supplement to Annals of Academy of Medicine. Singapore. 1976; 5:3,114.

25. Barlow DH, Beevers DG, Hawthorne VM, Watt HD, and Young GAR: Blood pressure measurement at screening and in general practice. Brit Heart J, 1977; XXXIX:1,7.

26. Hawthorne VM: Epidemiology and treatment of hypertension in the community, Current Med Res Op. 1977; 5, Suppl:109-14.

27. Hawthorne VM, and Sprent P: The British Aluminum Company, Locaber and Kinlochleven works, Scotland, report on the 1977 health survey, 1977.

28.Ballantyne D, Clark A, Dyker GS, et al.: Prescribing exercise for the health. Assessment of compliance and effects on plasma lipids and lipoproteins. Health Bulletin, 1978, 169.

29.Bryers F, and Hawthorne VM: Screening for mild hypertension: costs and benefits. J Epid Comm Health, 1978; 32:3, 171.

30.Hawthorne VM, Fry JS: Smoking and health: The association between smoking behaviour, total mortality, and cardiorespiratory disease in west central Scotland. J Epid Comm Health, 1978; 32:4, 260.

31.Hawthorne VM: Multiphasic screening. Occupational Health 1979: 178.

32.Barber JH, Beevers DG, Fife Retal.: Blood pressure screening and supervision in general practice. Br Med J 1979; I:843.

33.Hawthorne VM, and Gilmour H: Relationship of glucose to prevalence of ECG abnormalities at baseline and to 6-yr. mortality in Scottish male aged 45-64 yr. J Chron Dis 1979; 32: 787.

34.Hawthorne VM, Murdoch RM, Womersley J: Body weight for men and women aged 40-64 years from an urban area in the west of Scotland. Comm Med 1979; I:229.

35.Isles C, Brown JJ, Cumming AMM, et al.:Excess smoking in malignant-phase hypertension. Br Med J, 1979; I:579.

36.Hawthorne VM: Epidemiology of respiratory disease. Medicine 1979; 23:1158-1162.

37.Beevers DG, Hawthorne VM, Padfield PL: Salt and blood pressure In Scotland. BMJ 1980; 281:641.

38.Hole DJ, Clarke JA, Hawthorne VM, Murdoch RM: Cohort follow-up using computer linkage with routinely collected data. J Chron Dis 1981; 34: 291-297.

39.International Collaborative Group, circulating cholesterol level and risk of death from cancer in men aged 40-69 years. JAMA 1982; 248:2853-2859.

40.Garn SM, Shelly D Pesick, Hawthorne VM: The bony chest breadth as a frame size standard in nutritional assessment. Am J Clin Nutr 1983; 37:315-318.

41.Hawthorne VM. Preventing cardiovascular disease for the nineties: Practical policies for the present. Scott Med J 1983; 28:7-16.

42.Garn SM, , Hawthorne VM, Pilkington JJ, Pesick SD: Fatness and mortality in the west of Scotland. Am J Clin Nutr 1983; 38:313.

43.Gillis CR, Hole DJ, Hawthorne VM, Boyle P. The effect of environmental tobacco smoke in two urban communities in the west of Scotland. In environmental tobacco smoke. Eds. R. Rylander, Y Peterson, CN Snelki, European J Resp Dis 1984; suppl 133, 65:121-6.

44.Hawthorne VM. Tuberculosis, respiratory and cardiovascular risks of dying in the Renfrew District of Scotland: a report to the trustees of the Renfrewshire Memorial to the Late King Edward VII. 1985.

45.Isles CG, Walker LM, Beevers GD, et al.: Mortality in patients of the Glasgow Blood Pressure Clinic. J of Hypertension 1 986; 4;141-156.

APPENDIX D

TRENDS IN MORTALITY FROM STROKE IN SCOTLAND 1950 TO 1986

The purpose of this study was to compare stroke mortality trends in Renfrew and Paisley cohort and national basis to evaluate the effect of the hypertension control clinic established in Renfrew and Paisley on trends of stroke mortality. Due to the small number of stroke-related deaths in this cohort the stroke mortality trend could not be determined. However, for consistency of text this paper has been put in a separate appendix.

APPENDIX D

TRENDS IN MORTALITY FROM STROKE IN SCOTLAND, 1950 TO 1986

SUMMARY: The Scottish Registrar General's Annual Reports have been used to study trends in stroke mortality in Scotland during 1950-1986 in those aged 45 to 74. In 1950 the age-adjusted mortality rate for cerebrovascular disease was 347.4 per 100,000 population for men and 360.8 for women falling to 199.6 for men and 155.8 for women in 1986; higher rates were observed at older ages for both men and women. This downward trend has accelerated from 1976 for males. The average annual decline in age-adjusted mortality from stroke over the 37 year period was 4.0 per 100,000 in males and 5.5 in females. This reduction in death rates was proportionally higher, in all age groups over 55 years, and in women rather than men. There are no data documenting a decline in the prevalence of hypertension in the population, but both detection and the ability to treat and control hypertension have improved markedly over recent years. A concomitant decrease in the severity of epidemic respiratory infection, improved diet and social and economic changes, better diagnosis and treatment of stroke and associated hypertension, and a decrease in smoking may have contributed to the improvement in recorded death rates from stroke. Trends in mortality can be used in the evaluation of the impact of community based CVD prevention programme.

CONTENTS

APPENDIX D

INTRODUCTION

Cerebrovascular diseases are now the third leading cause of death in most developed countries and in addition lead to serious disability in the survivors. Analysis of mortality statistics undertaken in several countries during the past two decades suggests that deaths due to stroke are on the decline (335-338). This trend accelerated in the mid 1960's in U.S.A. (339) and early 1970 in Japan (340) but the reasons have not yet been fully explained. The decline could have been caused by a decrease in the incidence of stroke or improved survival rates or both. The most plausible explanation is that the incidence has fallen , although the evidence is as yet incomplete (340-342). Many workers attribute the decline to advances in the treatment of high blood pressure (343-345). Other factors suggested include changes in lifestyle and improvements in medical care (343). Antihypertensive drugs have been available since the early 1950s, although the range of agents and their acceptability have increased considerably over the past 15 years (346). In several countries the detection, treatment, and control of hypertension have improved considerably over the past two decades (344, 347). This report presents data on the secular trends in stroke mortality in Scotland, during the period of 37 years from 1950 through 1986 and discusses possible causal factors.

POPULATION AND METHOD

Population: Between 1950 and 1986 a total of 71,031 men and 81,445 women aged 45 to 74 died from stroke. Table

APPENDIX D

1 shows the total number of deaths from stroke by year of occurrence in Scotland. Death rates for persons aged 45-74 were examined to assess the impact of premature mortality from stroke. On the other hand, because of the problems of diagnostic reliability in the elderly, deaths amongst people over 75 years have been excluded. People aged under 45 are excluded from the analysis presented since the number of deaths is too small at these ages to form the basis of a reliable statistical analysis.

Method: The data on deaths for the years from 1950 to 1986 were obtained from the Registrar General's Annual Statistical Report for Scotland (Registrar General 1950-86). The Sixth Revision (1950 to 1958), Seventh Revision (1959 to 1967), Eighth Revision (1968 to 1978) and Ninth Revision (1979-86) of the International Classification of Diseases and Injuries and Cause of Death (ICD) had been used for cause of death in mortality statistics. The Sixth and Seventh Revision rubric for stroke included ICD Nos. 330-334, (Vascular Lesions Affecting the Central Nervous System) and was transferred, in the Eighth and Ninth Revision, to ICD Nos. 430-438 (Disease of Circulatory System, cerebrovascular diseases). The comparability ratio for the change of classification from the Seventh to Eighth and Eighth to Ninth Revisions was estimated as 0.988 and 1.043 respectively by the Registrar General in Scotland (348). The comparability ratio was not used for this analysis and the data was considered as a part of continuous trend. The denominator population used was that calculated by the Registrar General on the basis of census

data, updated yearly by the use of birth and death notifications and information on migration.

Regional variation: To examine regional variations in mortality trends from stroke, Scotland can be divided into four geographical divisions based on Health Board Areas. These are made up as follow.

North Division: Highland, Orkney Islands, Shetland Islands.

West Division: Argyll and Clyde, Ayrshire and Arran, Western Isles and Greater Glasgow.

East Division: Grampian, Tayside, Fife, Lothian, Borders.

Central Division: Forth Valley, Lanarkshire, Dumfries and Galloway.

Mortality data for each of the fifteen health board areas were combined to form the four geographical regions. The figures were extracted for each year from 1974-1986, taking into account the introduction of a new regional structure, making a thirteen year period in total.

ANALYSIS

Mortality rates were adjusted for age and gender by the direct method using the 1981 Scottish population as standard. Age adjustment was based on three age categories: 45-54, 55-64, 65-74. The entire study period of thirty-seven years was divided into seven quinquennia and one 2 year period to investigate the rate of change in the observed trends. A least squares linear regression line was fitted for each gender for the entire thirty-seven year period and for each quinqennium (349, 350). T-Tests were performed to ascertain whether the estimated slope of the line was significantly different from zero

(350). Absolute and percentage changes in mortality were calculated by expressing the difference between first and last quinquennia as a percentage of the first quinquennia. The estimation of lives saved was made by multiplying the difference between the 1950-54 and 1980-84 age specific rates in 10 year intervals by the appropriate 1980-84 population and summing the number of deaths in each group.

RESULTS

Time Trends for All Causes of Death

Table 2 presents the age specific and age standardised mortality rates per 100,000 population, percentage changes, slope, and T in the age specific and age standardised rates from all causes, for both males and females for the period 1950-1984. In men aged 45-74 the age-adjusted mortality rate from all causes in Scotland tended to increase slightly until 1965 after which it started to decrease. The rate for females decreased consistently from 1950 showing a larger fall than males, (24.3% compare to 12.3%). As a result the male/female ratio increased from 1950 to 1975 and after that started to decline. The age specific all causes death rate increased with advancing age in both males and females with males having a higher mortality rate than females of the same age. The slope of the best fitting linear regression line of death rate over the period 1950-86 was statistically significantly different from zero for all ages and for men and women except men 65-74 years old.

Time trends for cerebrovascular disease mortality

Figure 1 shows the secular trends, in the age

APPENDIX D

standardized and age gender specific mortality rates from stroke for men and women aged 45-74, on a semi-logarithmic scale so that proportionate changes can be compared between genders and age groups. Table 1 presents the trend in annual crude and age standardized mortality rates per 100,000 population for the period 1950-86, also, the male/female age adjusted rate ratio for each subsequent year. Also, cerebrovascular disease deaths have fallen in both males and females when expressed as a percentage of all deaths for the period 1950-86. These downward trends are highly significant in both genders ($P<0.0001$). Table 3 illustrates the absolute and percentage changes and slope of the age-adjusted mortality rate. In men the age adjusted mortality rate from cerebrovascular disease in Scotland, estimated by the slope of the linear regression, tended to increase slightly from 1950 to 1955, this increase was not significant, and after 1956 the slope of the linear regression started to decrease. This decreasing trend accelerated in 1976. The rate in females shows a reduction during 1950-86 and a larger fall than males. The average annual decrease was 4.0 per 100,000 males and 5.5 for females. Table 4 and Figure 1 show the trend in mortality rates for the age-gender specific group and also Table 4 displays the decline in the six age-gender categories as indicated by the value of regression slope and T. The age and gender specific death rates increase with increasing age in both genders. A ten year rise in age is accompanied by about a three to fourfold increase in mortality. Apart from 1950-52 the rates are higher in males than in females. This differences is most pronounced

above 55 years of age. Rates are up to 33% higher in men than among women over 55 years of age, with the exception of 1950-52. Both of these findings are consistent with that found in other studies.

Change in trends: Rates for every age gender group decreased with females experiencing the larger fall and the size of the decrease was statistically significant for all groups.

From 1975 to 1986 the fall in mortality accelerated in males. The percentage changes for the whole period of 1950-86 was 56.8% in women and 42.5% in men.

Avoidance of premature death: The impact of the falling mortality rates from stroke on premature death from 1950-54 to 1980-84, can be estimated by applying the 1950-54 age specific rates to the appropriate age categories in 1980-84. In the whole population, an additional 12,500 persons aged 45-74 would have died from cerebrovascular disease in 1980-84 if the 1950-54 rates had persisted.

Regional variation

Age-adjusted mortality trends in the four geographic regions of Scotland from 1974 to 1986 are presented in Table 5. The age-adjusted mortality rate from stroke were highest in central and west and lowest in the east region for all thirteen years of observation. These findings are compatible with other reports on regional variations in ischaemic heart disease and stroke in Scotland (20) and more widely throughout Britain (25).

APPENDIX D

DISCUSSION

The main finding of this study is a decline in age specific and age adjusted mortality rates from stroke in Scotland over the years 1950-86. This decline accelerated after 1975 for males and has resulted in the substantial saving of lives estimated at 12,500 in 1980-84, among the middle-aged population.

While being an invaluable data source for epidemiology, official mortality statistics may suffer some biases which should be taken into account. These errors are well documented (290, 353-356). If these errors are constant in magnitude between years and between the subgroups of the population under consideration, then mortality data may furnish valuable epidemiological information, providing an inexpensive and convenient means of obtaining clues to aetiological hypotheses and determining consistency between hypothesis. Artifacts due to revision of International Classification of Disease and change in the diagnostic fashion must be taken into consideration in assessing the long term variations in the frequency of disease. In Scotland the autopsy rate is relatively low (333) and the diagnosis of cerebrovascular accidents is based purely on clinical evidence with usually no attempt being made to distinguish between cerebral haemorrhage and thrombosis. On the other hand, it has been concluded that although the sub-diagnosis (type of stroke) was unreliable, stroke diagnosis as a whole was consistent and reliable (332, 357). Consequently, no distinction has been made in this paper. Epidemiological analyses of vital statistics data must always contend with

the problem of their validity. The antemortem diagnosis of stroke rests primarily on the evaluation of signs and symptoms rather than on laboratory measurements (358). Furthermore, the observed clinical event localizes the site of the lesions rather than their cause. Other forms of cardiovascular disease particularly hypertension, often accompany stroke (243), and the designation of cause of death depends on the judgement of the certifying physician. Diagnostic fashions in death certification change over time. The significance of secular trends of sub-types of cerebrovascular disease is especially open to question, given the difficulties often present in distinguishing between atherothrombotic brain infarction, embolism, intracerebral and subarachnoid haemorrhage (359, 360). Even considering deaths, from cerebrovascular disease as a single entity, as was done in this report, the possibility exists that the burden of stroke deaths could have been shifted to other rubrics of cardiovascular disease classification (336, 359, 360). However, the falling mortality trend seen in this study is consistent to the pattern of decline in stroke mortality in most industrial countries (343). Similarly the strong relationship with age in both males and females and the higher age specific mortality rates for males found in this study reflect the findings in some previous reports (335, 352). Since 1979 mortality from stroke has declined every year for each gender; before that period the pattern was less consistent. A broad change in overall mortality, rather than an abrupt amelioration of any specific disease

process leading to death from stroke could be responsible for this phenomenon, there has been decline in age-specific and age-adjusted all causes death rates from 1965 in males and 1950 in females. A considerable change also, occurred in overall mortality in the same period but, change in stroke mortality is more marked. However, consideration of the differences between male and female trends and its comparison with trends in all causes mortality in the two genders suggest that at least part of the large declines registered in male and female cerebrovascular disease mortality may be due to a decline in overall causes of death and particularly respiratory infections decline. Change in mortality could result from a decline in the number of high risk individuals in the population e.g. persons who suffered a non-fatal stroke, could in part , account for the fall in death rate from respiratory infection. Environmental factors may be important determinants of both short and long term variations in mortality rates. For example the fact that mortality rates for stroke in 1979 are higher than for neighbouring periods may be attributed to the severe winter of 1979, which in Scotland, brought the lowest temperature and heaviest snowfalls since the winter of 1962/63 (348), and which was associated with high mortality rates for many conditions. Similarly, the unexpectedly low rate in 1977 coincided with a mild winter, in which, the total hours of sunshine were above average in most areas. The west of Scotland had the highest totals for the year and in the Glasgow area the period May to August was the driest and sunniest since

records began around 100 years ago (361).

The greater decrease in stroke mortality observed in women may be related to differences in the treatment rates between males and females. For example, in New Zealand more women than men are currently receiving antihypertensive treatment (347). Different risk factors may be involved in the pathogenesis of cerebrovascular disease (362). The most important risk factors are ageing and hypertension. The risk of dying from stroke is most clearly related to hypertension with a smaller contribution from the other established major cardiovascular risk factors (363, 364). The continued decline in stroke mortality may be the result of more efficient treatment and effective control of hypertension, to reductions in the risk of stroke among persons with hypertension or a decline in hypertensive disease in the population secondary to changes in the risk factors for elevated blood pressure (336, 365). The possible influence on secular trends of other potential risk factors for stroke such as raised serum lipids and blood glucose, oral contraceptives, diet and cigarette smoking has not been investigated systematically. Stroke Council Report suggest that these risk factors do not have consistently strong association with stroke (366), however this does not agree with our results based on a cohort study in Renfrew and Paisley in West of Scotland. In this study based on logistic regression model show that stroke mortality is strongly associated with age, blood pressure level, impaired glucose metabolism, cigarette smoking and

negative association with obesity but there are no connections with serum cholesterol. Diabetes accelerates the atherosclerotic process, but there is a low relative risk of stroke in non-hypertensive diabetics (366). Furthermore, there is no evidence of a decline in the prevalence of diabetes and there is no evidence that major improvement in its management has resulted in a major decrease in mortality.

There has been an acceleration in the decline of tobacco consumption in Scotland since the mid 1970s (368-371), and a reduction in the use of cigarette with high tar content which, together, may contribute to the downward trend in stroke mortality. Changes in dietary patterns, including the general decline in the household use of animal fats and refined sugar and an increase in the use of vegetable fats and margarine, have been discussed by flory et al. (371) in relation to heart disease.

The mortality from coronary heart disease and mortality from all cardiovascular disease are known to show considerable regional variation in Scotland (20, 25). The rates are low in the east part of the country and gradually increase westwards and northwestward. Much less is known of the regional variation in morbidity and mortality from cerebrovascular diseases. According to this regional analysis, mortality from stroke is highest in central and west part of the country. There are, in general, higher rate in the west-central compared to the east side of the country for each consecutive year since 1974.

APPENDIX D

Stroke is primarily a disease of the elderly; in 1985 65% of all stroke deaths occurred in persons age 75 and over. Neverthless, more than a third of fatal stroke events occurred before age 75, therefore detailed examination of the mortality trends for persons under the age of 75 is also warranted. With the extension of average life expectancy to 70 years for males and 75.8 years for female in 1985 in Scotland (350) death among persons under 75 can be considered to represent premature mortality from a public health point of view.

In conclusion, the age-adjusted and age gender specific death rate from cerebrovascular disease in Scotland has been decreasing since 1956. Improved care for different primary risk factors associated with stroke such as control of hypertension and change in the dietary habits and smoking have been proposed as the major reasons for the declining mortality. This suggestion is supported by several intervention studies showing that effective treatment of hypertension reduces cardiovascular complications, particularly stroke (372, 373). If the observed age adjusted time trends for the mortality of stroke, show the same pattern in people over 75 as well, in the future this will have a great impact on the resources for health care. Particularly as in Scotland as well as most other industrialised societies, this group of patients consumes more resources in terms of hospital days than any other diagnostic group in departments of medicine.

The observed age-adjusted time trends can be used to

predict future patterns of premature death from stroke and to evaluate the additional impact, if any, of community based cardiovascular disease prevention programmes.

APPENDIX D

TABLE 1. Age Adjusted and Crude Death Rate Per 100,000 Population and Number of Death from Cerebrovascular Disease and Stroke Death as a Percentage of all Deaths by Gender, Age 45-74, Scotland, 1950-1986.

Year	No. of Death		Age Adjusted Death Rate		Crude Death Rate		stroke as a % of All Death		M/F Age-Adjusted Rate Ratio
	Male	Female	Male	Female	Male	Female	Male	Female	
50	1985	2621	347.4	360.8	293.5	318.1	11.5	18.0	0.96
51	2107	2723	362.5	369.4	307.4	331.2	11.9	18.2	0.98
52	2052	2641	357.1	356.1	296.9	318.3	12.1	18.7	1.00
53	2012	2552	357.4	342.8	292.6	307.2	12.2	19.3	1.04
54	2024	2251	359.1	365.4	291.0	268.3	11.8	20.0	0.98
55	2082	2700	371.1	357.9	295.4	318.8	12.2	19.4	1.04
56	2103	2600	370.6	341.0	296.4	305.0	12.1	18.9	1.09
57	2039	2517	356.6	326.2	384.4	292.9	11.6	18.6	1.09
58	2026	2653	352.1	339.9	279.6	306.7	11.5	19.3	1.03
59	1952	2594	339.9	329.3	267.4	297.4	10.8	18.7	1.03
60	2109	2405	361.4	303.4	286.4	273.9	11.8	17.7	1.19
61	1965	2602	337.2	325.2	267.9	296.5	10.7	18.5	1.04
62	1960	2364	334.9	294.7	267.7	269.9	10.7	17.3	1.14
63	1941	2419	331.1	295.0	266.5	275.8	10.0	17.1	1.12
64	2098	2454	360.3	297.2	288.3	280.7	11.4	18.2	1.21
65	2038	2540	335.5	303.4	277.9	288.1	10.7	18.6	1.10
66	2003	2427	322.5	286.0	271.6	274.1	10.7	17.5	1.13
67	1896	2363	300.0	275.5	256.9	266.0	10.6	18.2	1.09
68	1976	2333	308.3	269.3	266.5	262.6	10.5	17.0	1.14
69	2002	2358	307.7	269.4	269.5	265.4	10.3	16.8	1.14
70	1957	2268	296.6	257.5	263.7	255.7	10.0	16.5	1.15
71	2071	2257	311.2	254.8	279.6	255.0	10.9	16.9	1.22
72	2155	2144	320.4	239.5	289.2	240.8	10.9	15.5	1.34
73	2162	2153	317.3	238.0	289.6	241.1	10.8	15.8	1.33
74	2083	2160	303.4	238.0	278.9	242.3	10.6	15.7	1.27
75	2134	2083	308.6	228.5	286.6	234.5	11.0	15.8	1.35
76	1991	2016	285.9	221.2	268.0	227.9	10.1	14.8	1.29
77	1731	1854	248.6	203.9	233.8	210.7	9.3	14.2	1.22
78	1770	1870	254.5	205.7	240.4	214.1	9.2	13.6	1.24
79	1874	1888	270.1	207.7	256.1	217.9	9.7	14.0	1.30
80	1745	1627	251.8	180.6	239.9	189.2	9.6	12.7	1.39
81	1688	1722	241.0	192.9	229.0	200.6	9.4	13.3	1.25
82	1563	1608	226.9	181.1	214.1	187.9	8.7	12.6	1.25
83	1509	1513	216.9	172.3	206.9	177.6	8.7	12.1	1.26
84	1431	1416	213.9	164.2	197.0	167.3	8.5	11.8	1.30
85	1449	1404	214.9	162.1	200.2	166.9	8.6	11.5	1.32
86	1348	1345	199.6	155.8	187.3	161.2	8.2	11.4	1.28

APPENDIX D

TABLE 2. Trends in Age-Specific and Age-Adjusted Overall Causes Death Rates/100,000 Population , Scotland 1950-86.

Year	Male				Female				M/F Age-Adjusted Rate Ratio
	45-54	55-64	65-74	Adjusted Rate	45-54	55-64	65-74	Adjusted Rate	
50-54	980	2580	5690	2875	620	1480	4000	1880	1.53
55-59	930	2530	5870	2891	540	1380	3760	1748	1.65
60-64	930	2580	5950	2931	540	1310	3550	1664	1.76
65-69	880	2460	5790	2825	540	1240	3300	1568	1.80
70-74	890	2420	5810	2821	550	1270	3080	1520	1.86
75-79	880	2310	5590	2716	530	1270	2990	1487	1.83
80-84	780	2150	5230	2521	470	1200	2930	1423	1.77
85-86	706	2079	5055	2420	402	1178	2943	1394	1.73
Percentage Change Between 50-54 and 80-84									
	-20.4	-16.7	-8.1	-12.3	-24.2	-18.9	-26.7	-24.3	-
Slope£									
	-5.3	-13.5	-14.8	-10.9	-3.3	-7.8	-37.3	-14.5	-
t$	-5.1**	-5.5**	-2.0	-3.5*	-3.1*	-4.5**	-11.8***	-10.6***	

£Slope of the regression line where the dependent variable is age specific or age adjusted rate and the independent variable is year.
*P<0.05, **P<0.01, ***P<0.001

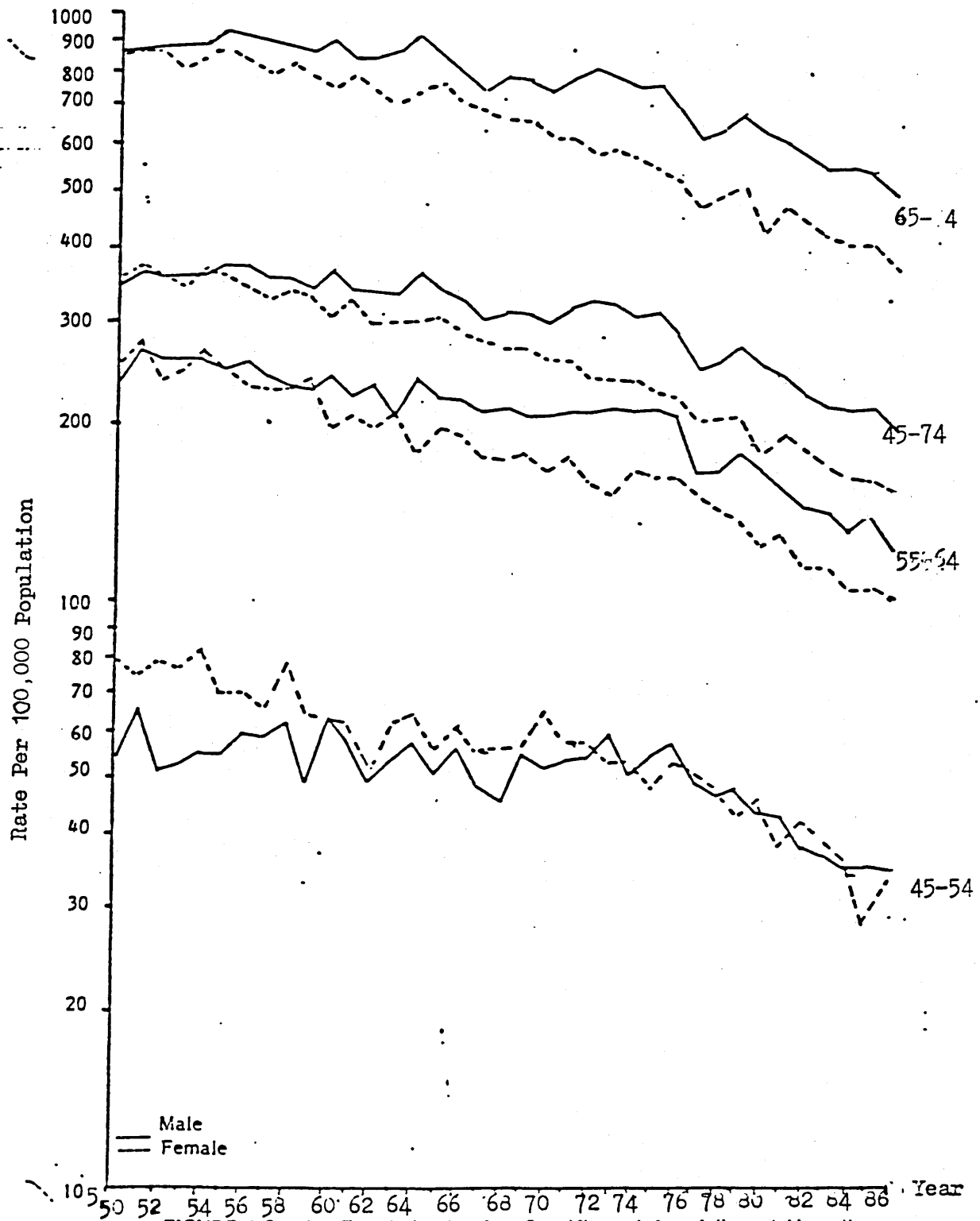


FIGURE 1.Secular Trends in the Age-Specific and Age-Adjusted Mortality Rates from Stroke. Persons 45-74. Scotland by Sex. Rate Per 100.000.

APPENDIX D

TABLE 3. Absolute Changes$, Percentage Changes and Slope@, Age-Adjusted Mortality Rates Cerebrovascular Disease, Scotland, 1950-86.

Year	Male				Female			
	Change in Rate	% Change in Rate	Slope&	t	Change in Rate	% Change in Rate	slope	t
50-55	+23.7	+6.8	+3.1	+2.3NS	-2.9	-8.0	-1.1	-0.5NS
55-60	-9.7	-2.6	-4.1	-1.7NS	-54.5	-15.2	-8.4	-3.4*
60-65	-25.9	-7.2	-0.8	-0.2NS	0.0	0.0	+2.5	+0.8NS
65-70	-38.9	-11.6	-6.6	-3.1*	-45.9	-15.1	-8.1	-6.4***
70-75	+12.0	+4.0	+1.0	+0.4NS	-29.0	-11.3	-5.6	-5.7**
75-80	-56.8	-18.4	-9.3	-2.2NS	-47.9	-21.0	-7.9	-4.1*
80-86	-52.2	-20.7	-7.9	-7.8***	-24.8	-13.7	-5.5	-4.9**
50-86	-147.8	-42.5	-4.4	-15.2***	-205.0	-56.8	-6.0	-36.1***

@Slope of the regression line where the dependent variable is age-adjusted rate and the independent variable is year.
$Absolute changes in rates are expressed per 100,000 per year, see Table 1 for the actual rates.
*P<0.05, **P<0.01, ***P<0.001
NS=not significant

APPENDIX D

TABLE 4. Trends in Age ,Gender Specific Death Rates (Per 100,000) and Measure of Change Over the Period 1950-54 to 1980-84 from Cerebrovascular Disease, Scotland, 1950-86.

Year	Male			Female		
	Age at Death			Age at Death		
	45-54	55-64	65-74	45-54	55-64	65-74
1950-54	67.8	255.8	868.5	78.8	257.6	845.1
1955-59	57.1	240.5	890.6	69.8	236.0	812.2
1960-64	56.3	228.4	861.0	60.6	200.3	736.2
1965-69	51.3	213.7	778.0	57.0	184.0	687.6
1970-74	53.8	209.0	764.2	57.2	163.9	588.5
1975-79	51.2	184.4	669.6	48.5	151.6	501.9
1980-84	42.0	149.0	576.4	40.2	116.9	431.4
1985-86	36.5	134.3	517.3	31.3	104.1	390.8
1950-54 To 1980-84						
% Change	-38.0	-41.7	-33.6	-49.0	-54.6	-48.9
Slope@	-0.7	-3.3	-10.6	-1.3	-4.3	-13.8
t	-6.5*	-12.2**	-8.8**	-11.2**	-21.4**	-20.8**

@Slope of regression line where the dependent variable is age-specific death rate and the independent variable is year.

*P<0.001, **P<0.0001

APPENDIX D

TABLE 5. Age-Adjusted and Percentage Change Mortality Rate, Cerebrovacular Disease, 1974-1986, four Regions of Scotland. Rate Per 100,000.

Year	Region							
	Central		West		East		North	
	No. of Death	Death Rate*	No. of Death	Death Rate	No. of Death	Death Rate	No. of Death	Death Rate
1974	794	302.7	1670	262.8	1600	248.2	179	265.7
1975	747	281.7	1720	276.0	1400	215.5	194	285.8
1976	684	263.0	1496	258.8	1464	219.4	174	256.7
1977	662	243.4	1434	232.1	1358	207.8	151	219.7
1978	669	244.5	1448	235.9	1373	210.4	150	219.6
1979	701	256.9	1485	242.2	1417	218.5	159	235.6
1980	657	239.5	1270	208.9	1298	201.1	147	216.2
1981	642	229.9	1337	226.7	1281	224.9	150	203.9
1982	569	203.5	1266	216.3	1187	179.2	163	231.1
1983	563	191.6	1204	208.9	1095	172.2	128	182.8
1984	482	174.5	1135	201.1	1101	176.2	129	188.1
1985	562	200.7	1106	181.0	1074	171.0	111	160.6
% changes								
1974-80		-20.9		-20.5		-19.0		-18.6
1980-85		-16.2		-13.3		-15.0		-25.7
1974-85		-33.7		-31.1		-31.1		-39.5

*Age-adjusted rate using the 1981 Scottish population.