UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HEALTH AND BIOLOGICAL SCIENCES

School of Medicine

A Community Study of Newly Diagnosed Type 2 Diabetes - Incidence, Cardiovascular Risk and Early Mortality. The Poole Diabetes Study.

By

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Thesis for the degree of Doctor of Medicine

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ABSTRACT

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A COMMUNITY STUDY OF NEWLY DIAGNOSED TYPE 2 DIABETES - INCIDENCE, CARDIOVASCULAR RISK AND EARLY MORTALITY. THE POOLE DIABETES STUDY.

By Rustom Noshir Guzder

Observational and experimental studies have complementary roles in defining optimal care for people with chronic disease. This is particularly relevant to type 2 diabetes which is a leading and increasingly important determinant of health care costs and health outcomes. Since, type 2 diabetes in the UK is predominantly diagnosed and managed in primary care, there is a dearth of information about the epidemiology of the disease. Hence, geographically relevant epidemiological studies which do not select patients from either primary or secondary care are of paramount importance in defining the burden of the disease and establishing possible causal associations. People with newly diagnosed diabetes are grossly underrepresented in the literature.

The Poole Diabetes Study commenced in 1996 to investigate the prevalence of diagnosed type 2 diabetes in a defined community. As part of this original study, a surveillance programme identified all new cases of type 2 diabetes in a defined population diagnosed between 1, May 1996 and 30, June 1998. From March 2000, I undertook to review all hospital, primary care and laboratory records to confirm the diagnosis of diabetes based on 1985 WHO criteria. Based on these numbers, I have calculated the age/sex adjusted annual incidence of diagnosed type 2 diabetes to be 1.67/1000. Extrapolating to the UK, the estimated annual incidence is 98,000 or 265 cases diagnosed per day.

In July 2001, I undertook a further review of all records and physical examination of available survivors to establish outcomes. I evaluated the performance of the Framingham and UKPDS cardiovascular and coronary heart disease risk calculators demonstrating that at the level of the individual, these calculators have modest discrimination and poor calibration. I have shown that the metabolic syndrome is associated with a twofold hazard of primary cardiovascular disease in people newly diagnosed with type 2 diabetes and disease-free survival incrementally worsens with the number of features present. The mortality data shows that people with newly diagnosed type 2 diabetes have an approximate doubling in their odds of dying. The increased risk is seen in all age groups, including the elderly, and for all causes of mortality. Early mortality in middle-aged women appears to be most affected by a diagnosis of type 2 diabetes. I have explored the relationship between geographic deprivation indices and both cardiovascular disease and early mortality showing that there is a strong and consistent association and have documented the lack of association between mild to modest reductions in calculated glomerular filtration rate at diagnosis and early mortality in type 2 diabetes.

I hope that by defining disease burden, particularly cardiovascular and mortality outcomes and the predictors of these outcomes in people with newly diagnosed type 2 diabetes, this study will help establish the basis for intervention trials and the development of risk calculation tools and clinical services for individuals who develop type 2 diabetes in the future.

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Abbreviations

95%CI	95 percent confidence interval
ATP	Adult Treatment Panel
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
BSA	Body surface area
CG	Cockcroft-Gault
CHD	Coronary Heart Disease
CKD	Chronic kidney disease
CVD	Cardiovascular Disease
DES	Diabetes Education Sessions
DM	Diabetes mellitus
DOH	Department of Health
eGFR	Calculated glomerular filtration rate
GFR	Glomerular filtration rate
HDLc	Low-density lipoprotein cholesterol fraction
HR	Hazard ratio
ICD	International Classification of Diseases
K/DOQI	Kidney Disease Outcomes Quality Initiative
LDLc	Low-density lipoprotein cholesterol fraction
MDRD	Modification of Diet in Renal Disease
MetS	Modified NCEP-criteria metabolic syndrome
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Survey
NHS	National Health Service
NICE	National Institute for Clinical Excellence
NKF	National Kidney Foundation
NSF	National Service Framework
ODPM	Office of the Deputy Prime Minister
ONS	Office of National Statistics
OR	Odds ratio
ROC	Receiver operating characteristic

SMR	Standardised Mortality Rate
TC	Total cholesterol
TC/HDL	Total cholesterol:HDL cholesterol ratio
TG	Serum triglycerides
UK	United Kingdom
UKPDS	United Kingdom Prospective Diabetes Study
VPT	Vibration perception threshold
WHO	World Health Organisation

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Phil Wallace extracted vast quantities of information from the hospital diabetes database at my request. His contribution is much appreciated.

In particular, I must acknowledge the vast contribution of Sue Budd who recruited the original cohort as part of her work on the prevalence of diagnosed diabetes. Her ability and personality reflects itself in the continued contribution of the cohort members over the five years of the study, the minimal dropout rate, and the vast quantity of baseline data that could be accessed.

I must thank Rosemary White for introducing me to the practice staff. She and Jayne Cox in their roles as research nurses ably supported my efforts throughout. I would like to acknowledge Jo Begley for arranging access to the original biochemistry database at Poole Hospital.

I would like to thank the secretaries and reception staff at the Poole Diabetes Centre, who helped so greatly with the administrative work and

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I must acknowledge the efforts of all the GPs and practice nurse associated with the study who gave so freely of their valuable time and expertise.

In particular, I must thank the patients, who for no pecuniary or ancillary benefit attended review visits, often at their own cost, filled in numerous questionnaires, responded repeatedly to telephone calls and letters and allowed me into their homes. Their unwavering contribution fills me with great encouragement.

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CHAPTER 1

Background and general introduction

Diseases with the cardinal features of diabetes have been described in ancient medical texts from China, India and Greece. In 400 BC, a Chinese physician, Nei-jing, is believed to have described the symptoms of diabetes. Around the same period, an Ayurvedic physician in India, Sushruta, recognised an illness associated with sweet urine which he called *madhumeha* (honey-urine), a term that is still used in parts of India. In 6AD, another Ayurvedic physician, Charaka, described the illness in physically unfit and overweight individuals and drew a link with nutritional factors. His ancient medical text, Charaka Samhita, describes ".....an illness that afflicts the rich and is brought about by a gluttonous overindulgence of flour, sugar and oil". A view that seems to have been shared by the eminent 17th century British physician, Thomas Willis, who along with providing the remarkable suggestion of a link between diabetes and depression by stating that "diabetes is caused by melancholy" believed that the incidence of diabetes was on the rise and attributed this increase to "fellowship and the gusling down chiefly of unalloyed wine".

Areteus of Cappadocea, a Greek physician in the 1st century AD described diabetes as "relatively rare". However, the disease in the 21st century has taken on near-epidemic proportions. It has been estimated that, worldwide, by the year 2010, there will be around 220 million people with diabetes [1]. In the Poole area alone, prevalence studies of diagnosed diabetes undertaken in 1983 and 1996 have shown an 83.6% increase in prevalence [2].

The consequences of this increasing prevalence in terms of health resource allocation and costs to the NHS in the United Kingdom are enormous. In 1997, 8.7% of costs in the acute sector were spent on people with diabetes [3], which

translated to an expenditure of around £2100 on each resident with diabetes per year compared to around £300 on each person without diabetes. People with diabetes are four times as likely to undergo a cardiac revascularisation procedure as compared to those without diabetes and the annual cost (1995 prices) of in-hospital care of coronary heart disease in people with diabetes is estimated to be over £1 billion [4]. Additionally, little data is available on costs of diabetes management in primary care. This is likely to be substantial as the majority of patient contact occurs in the community setting. However, the costs to society of diabetes go beyond those associated directly with the delivery of medical care. Indirect costs as a result of diabetes-related morbidity and disability leading to a loss of productivity are difficult to quantify.

Epidemiological studies of diabetes are able to quantify and describe the burden of disease, and provide relevant local data on the frequency of newly diagnosed diabetes and the changing prevalence of the disease. Furthermore, these studies can be used to generate research hypotheses and also help identify the outcomes and processes that should be adopted in an experimental study. In particular, a well-designed epidemiological study may identify and quantify the impact of putative "risk factors" for disease or disease complications. Identifying predictors and developing scoring systems from such studies enables a "risk-based" approach to therapeutic interventions as has been adopted for the primary prevention of coronary heart disease in the UK [5]. Such an approach may be cost-effective for the health service, allow targeting of therapeutic intervention at those individuals at highest risk, avoid the exposure of individual patients to unnecessary therapy and may, in certain circumstances, be more

effective at reducing disease rates at a population level [6]. In terms of providing useful epidemiological information, studies that reflect usual care may be preferable to results derived from populations entered into large experimental studies (randomised controlled trials). For instance, results from the UKPDS study cohort [7] have provided valuable insights to the early course of type 2 diabetes but generalisability and applicability of these results are limited by the exclusion criteria applied at the time of recruitment to the study, in particular, age restrictions, the exclusion of individuals with active coronary heart disease and the diagnostic criteria adopted in the study. Furthermore, since a large proportion of patients , particularly those considered to have uncomplicated type 2 diabetes, are managed in primary care, observational studies that include both primary care and secondary care patient populations are likely to provide a clearer picture of outcomes in the community.

The main criticism of the observational study design is that internal validity may be less than ideal and thus may not truly reflect causal relationships. The uneven distribution of unknown or unrecognised confounding factors between groups in such a study may affect the observed results.

Nonetheless, the two methods, experimental and non-experimental, are complementary in nature and have a significant role to play in advancing our understanding and management of diabetes mellitus.

> "Every research strategy within a discipline contributes importantly relevant and complementary information to a totality of evidence upon which rational clinical decision-making and public policy can be reliably based. In this context, observational evidence has provided and will

continue to make unique and important contributions to this totality of evidence upon which to support a judgment of proof beyond a reasonable doubt in the evaluation of interventions." [8]

There have been several epidemiological studies on diabetes published from the Poole area over the past fifteen years. Previous studies include establishment of the mortality rates for a diabetic population [9,10], prevalence of peripheral vascular disease and neuropathy [11-13], prevalence of proteinuria and microalbuminuria [14-16], and the overall prevalence of diagnosed diabetes [2,17].

Observational studies in people with newly diagnosed diabetes are able to answer questions regarding the reliability of diagnostic criteria, the prognosis for the individual concerned and factors affecting this prognosis. These questions inform therapeutic decision-making based on available experimental data (evidence-based interventions from randomised controlled trials etc.) in the clinic setting. A recent report from the Academy of Medical Sciences [18] and proposed changes to Department of Health research funding mechanisms [19] have stressed the importance of research aimed at driving effective clinical practice and observational studies are an important facet of this process.

In light of the surprising paucity of observational data in people with a new diagnosis of type 2 diabetes, in particular, data relating to the United Kingdom and pertaining to incident cardiovascular disease and early mortality, I undertook the research project described in this thesis.

Although further details are provided in the introduction to each chapter, a brief synopsis of the goals of the research are described below:

- One of the first steps in defining diabetes health care needs in a population is assembling information on the prevalence and frequency of diagnosis (as opposed to true incidence) of the disease. Furthermore, data on the frequency of diagnosis helps inform studies on the changing local prevalence of the disease (as increases in prevalence may relate to improved patient survival or population migration patterns as opposed to a true increase in disease appearance related to factors like increasing obesity in the background population, changing demographics with a more elderly population, or improved screening/diagnostic processes). Information on incidence also provides comparator data for other similar studies in different areas of the country. Hence, I have studied the incidence of *diagnosed* type 2 diabetes in a geographically-defined UK population in the area of Poole, Dorset.
- At the time of study inception, the 10-year Framingham CHD risk equation [20] was proposed as a tool for defining risk of incident cardiovascular disease both in people with and without diabetes [21]. During the course of the study the lipid treatment threshold for people with diabetes was reduced from a 10-year CHD risk of 30% to 15% [5,22]. Additionally, the UKPDS risk engine for CHD became available [23]. Although such absolute risk-based interventional approaches are theoretically attractive, these scoring methods used to assign risk must be effective both at the level of the population and at an individual level. Prospective validation studies of these risk

equations in people with diabetes had not been undertaken. Hence, I studied the overall predictive value, discrimination and calibration of these risk equations for incident cardiovascular and coronary heart disease in a community-based population with newly diagnosed type 2 diabetes.

- The metabolic syndrome, which comprises a constellation of cardiovascular risk factors, is of great interest as it is associated both with type 2 diabetes and clinical atherosclerosis. The impact of the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) metabolic syndrome [24] and its individual features on cardiovascular risk in people with diabetes has not been demonstrated within the setting of a prospective study. I have investigated the association of the presence of modified NCEP definition metabolic syndrome and its individual features on cardiovascular and coronary heart disease both in a cross-sectional analysis and in a prospective, five-year community-based study of people with newly diagnosed type 2 diabetes.
- Although markers of deprivation have been associated with both incident coronary heart disease and increased mortality in the general population [25], the impact of deprivation on incident cardiovascular disease in people with type 2 diabetes has not been studied. Furthermore, it is uncertain whether traditional risk factors explain any demonstrated increase in cardiovascular risk associated with deprivation. I have explored the relationship between

geographical indices of deprivation, traditional cardiovascular risk factors, the metabolic syndrome and incident cardiovascular disease in a prospective, five-year community-based study of people with newly diagnosed type 2 diabetes.

- Mortality data is important so as to define the burden of a disease process, to develop systems of health care delivery and to discuss prognosis in the clinical setting. Although, several studies have shown that diabetes is associated with a substantial increase in all-cause mortality, a large proportion of which is attributable to vascular mortality, studies of early mortality in people with newly diagnosed type 2 diabetes are not available. I have studied mortality patterns in people with newly diagnosed type 2 diabetes using a case-control study design with local controls. Additionally, I have investigated predictors of early mortality in this cohort based on available data at the time of study entry.
- Recently, there has been substantial interest in the adoption of methods to calculate glomerular filtration rate (eGFR) in the diabetes clinic setting. Two widely used methods are the abbreviated MDRD equation [26] and the Cockcroft-Gault formula [27]. It is unclear whether Cockcroft-Gault or MDRD values will add to the prediction of early mortality in people with a new diagnosis of type 2 diabetes, particularly in those identified to have mild to moderate reductions in eGFR. In this context, I have studied the agreement in derived values of the two methods of estimating eGFR and their ability to

predict early mortality in people with newly diagnosed type 2 diabetes. I have also studied whether eGFR values add to the known predictive value of age, proteinuria and other risk factors for early mortality

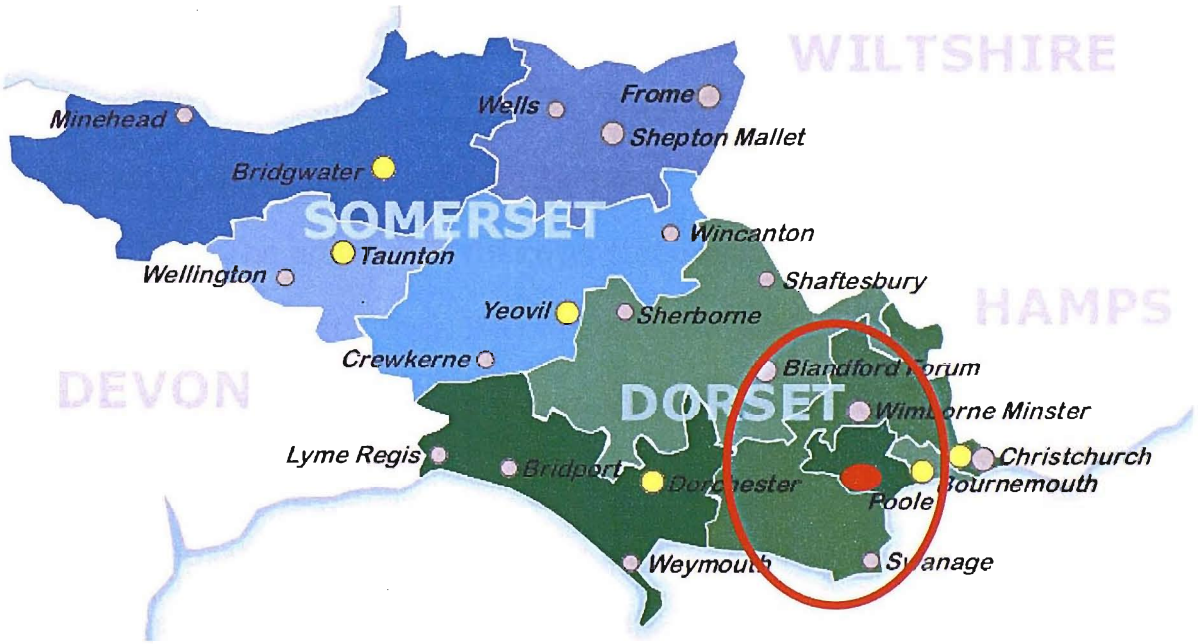
CHAPTER 2

Study methodology - general

Introduction

Demographics and Healthcare in the Poole area

Dorset and Somerset Health Authority (HA) district serves a mixed town and rural population in the south west of the United Kingdom. It is relatively affluent, but has a substantial population of people over the age of 65. Specialist diabetes services are provided by three large acute trusts, namely, Poole General Hospital, Bournemouth and Christchurch Hospitals, and Dorchester District General Hospital NHS Trusts.



The Poole area has a higher than average retirement age population (24% vs. England average 18%) and an ethnic population of less than 2% (England 9.1%) (*Data from ONS census 2001*). The median full-time annual pay in Poole in 2005

was £22,700 (England £23,300) *(Data from ONS Annual Survey of Hours and Earnings, 2005)*. In the Poole Hospital catchment area, 22 (6.5%) of the Enumeration Districts are within the most deprived 20% nationally. *(Data from ODPM Indices of deprivation, 2004)*. Unitary authorities in the Poole area have a female life expectancy at birth above that of England (82.1 vs.80.9 years), and a male life expectancy above than that of England (78.2 vs. 76.6 years) *(Data from ONS Life Expectancy at Birth 3-year rolling average 2002 – 2004)*.

Poole General Hospital Diabetes Centre

The hospital diabetes centre is a dedicated clinical area providing reception, clinic and secretarial space along with an education room and an in-house podiatry department. The centre runs a formal education programme for people with a new diagnosis of type 2 diabetes known as the Diabetes Education Service (DES). The programme runs over three separate sessions with specific educational components. Over 85% of people with a new diagnosis of type 2 diabetes in the hospital catchment area attend these sessions (unpublished data, Gatling W).

Since the late 1980s, the centre has maintained a computerised diabetes database (PROTON®, CCL, UK) although following a tendering process, the database has been switched to DIABETA3® (Vector, UK).

A patient-held record of diabetes care and measurements performed (both clinical and biochemical) in the primary and secondary care settings is in routine use. This record details changes in medication and the development of complications, as well.

Study Recruitment and Design - Overview

Recruitment of the Study Cohort

The original Poole diabetes study was established in 1996 to establish the prevalence of diagnosed type 2 diabetes in the local population and to monitor changes in prevalence since a previous study in 1983. The results of this study has been published [2,28].

As part of the above mentioned study, twenty-six GP practices, whose registered patients lived within the Poole hospital catchment area, were invited to take part in the extended Poole Diabetes Study. Practices on the boundaries of the catchment area were not asked to participate, as referral to neighbouring hospitals would affect the ascertainment of cases. Altogether, 24 computerised GP practices agreed to take part. Thus, the population in the study consists of all the patients, 186,889, registered with 24 primary care practices in the Poole area and representing 78% of the hospital's total catchment population. At the start of the study, the practice diabetes registers and hospital diabetes register were compared and manually updated by a research nurse so that the number of diagnosed patients with diabetes in the population was known and age-sex characteristics of the study population established. So as to avoid underestimating prevalence due to delayed referral to the education sessions or updating of the practice registers, a surveillance programme was established. This programme identified all cases of type 2 diabetes in the population diagnosed between 1, May 1996 and 30, June 1998. The programme (that was run by two research nurses) consisted of monitoring the weekly open access diabetes education programme for newly diagnosed patients with type 2

diabetes, the hospital inpatients through the dieticians, discharge prescriptions and the hospital diabetes clinics and in the GP practices, repeat prescription requests and letters. From June to December 1997 and at the end of the recruitment phase in June 1998, the hospital diabetes register was compared with the individual practice registers and updated. The hospital diabetes register includes information from all the hospital diabetes clinics and the primary care diabetic eye-screening programme undertaken by optometrists in high street practices [29]. Furthermore, the research nurses collected routine baseline data on these individuals as per the prevailing hospital clinic practice. A 12-lead electrocardiogram was performed using a Marquette ® ECG machine in those aged less than 75 years at diagnosis. Blood pressure was measured twice in the semi-recumbent position in the non-dominant arm with a mercury sphygmomanometer and the average reading noted. Body height and weight were measured. Body mass index (BMI) was calculated. Smoking history was ascertained. Smokers were defined as those who had smoked regularly during the previous twelve months. Date of birth and residence address was documented. Medical history and medication was collected on a standardised form. Foot examination was carried out and pedal pulses documented. Patients with absent foot pulses were offered further assessment by the hospital podiatry service. Vibration perception threshold (VPT) measurements were performed using a hand-held biothesiometer (Biomedical Instrument, Newbury, OH, USA) at the great toes and the average of three readings on each limb were recorded. A single fasting blood sample was drawn and HbA_{1c}, serum total cholesterol (TC), triglycerides (TG), and creatinine were measured. Lipid sub-fractions (HDL

cholesterol (HDL) and calculated LDL cholesterol (LDL)) were measured in individuals aged less than 75 years. All collected data was entered on the PROTON database.

In August 2000, I carried out a further review of the 24 general practice patient databases. Patients not present on the hospital register were carefully identified by manually comparing the hospital and practice diabetes lists and the hospital register was then updated. This updating process was undertaken to find any cases that might have been missed by the original surveillance programme. All patients presumed to have been diagnosed with diabetes between May 1st 1996 and June 30th 1998 were identified. Since biochemical analysis for all the practices are performed in the hospital laboratory, the patient hospital numbers for these individuals were matched to entries on the hospital biochemistry database and the results extracted. Manual matching of results was performed to establish a date of diagnosis of diabetes based on 1985 WHO criteria [30]. Cases of newly diagnosed diabetes were included if the 1985 WHO diabetes criteria were met, they were registered with a GP included in the study and they had type 2 diabetes defined by absence of ketonuria and not requiring insulin within one month of diagnosis. The date of diagnosis recorded was based on the first confirmatory laboratory glucose result. This process identified 748 individuals newly diagnosed with type 2 diabetes during the recruitment phase of the study. No exclusion criteria were applied at the time of enrolment. For patients diagnosed while admitted to hospital as in-patients, a confirmatory glucose reading within 3 months of the original sample was sought. Based on the this approach, ten members of the original cohort were classified

as stress-related hyperglycaemia since the diagnostic plasma glucose levels were ascertained in periods of acute illness and re-testing was non-diagnostic. Furthermore, Cushing's disease was diagnosed as the cause of hyperglycaemia in two cohort members within a year from diagnosis. After exclusion of these individuals, 736 individuals (403 men, 333 women) with a new diagnosis of type 2 diabetes were enrolled in the study. Cohort members were flagged on PROTON and each individual was assigned with a unique study number to create an independent dataset.

Recruitment of Study Controls

For the purposes of the planned mortality analyses, it was necessary to identify local age and sex matched controls. Practice lists were available from the time of original enrolment of the cohort. The next gender-matched, non-diabetic individual (not identified on either the practice or hospital diabetes register) within the same five-year age band on the alphabetically arranged general practice patient list was selected as a non-diabetic control and their details entered onto a separate PROTON dataset. Hence 736 individuals (403 men, 333 women) were flagged as age and sex matched controls. Besides for NHS numbers, as identifiers, no other information was collected on these individuals.

Registration of cohort and controls with the Office of National Statistics

The 736 cohort members and their controls were flagged with the Office of National Statistics to allow collection of mortality data. Furthermore, we were able to identify individuals who had moved out of the area and re-registered in a different part of the country.

Baseline Data Collection Methods

Baseline data was first extracted from PROTON based on the entries at the time of recruitment. I then interrogated the patient information systems (EMIS® and VAMP®) at each of the GP practices and extracted treatment data, blood pressure data, height and weight measurements along with updating individual address and telephone entries. The measurements were collated with the original study data if collected within 3 weeks of the diagnosis date. Additionally, data from the dietetics service was sought, as well. The biochemistry system at the hospital was used to extract all biochemistry data available on the cohort. An information leaflet was sent to each member of the study cohort and this was followed up by telephone contact by either the research nurse or me. A postal questionnaire was included to ascertain treatment data. Each individual was requested to return the questionnaire and their patient-held record diaries (see page 26) in an enclosed self-addressed envelope. After manual data extraction, these record diaries were posted back to the individual cohort members. Using these different approaches, I was able to establish complete baseline data collection in 716 cohort participants. I then coded the baseline electrocardiograms for left ventricular hypertrophy and probable myocardial infarction using the Minnesota coding system [31].

Review Process

Data collection for cardiovascular outcomes closed on July 1st, 2001. Pre-defined cardiovascular outcomes were evaluated (**Table 2.1**). However, mortality data was collected until September 30th, 2003. Along with the research nurse, I undertook an interview and clinical examination of those

surviving members of the cohort registered within the Dorset Health Authority. This contact was arranged by appointment in the hospital diabetes centre, the GP surgeries and as home visits (**Fig. 2.1**). During the review, the baseline data collection process was repeated. A 12-lead electrocardiogram was performed using a Marquette ® ECG machine. Blood pressure was measured twice in the semi-recumbent position in the non-dominant arm with a mercury sphygmomanometer and the average reading noted. Body height and weight were measured. In both the clinic and home settings electronic scales (Tanita ®) were used to ascertain weight. Height was measured with a portable stadiometer (Seca ® 214) in the hospital clinic setting and during home visits, and a variety of height rods in the general practice surgeries (a wall-fixed tape measure was used in three surgeries, as an alternative). Smoking history was ascertained. Medical history, clinical examination and medication history was collected on a standardised form. Foot examination was carried out and pedal pulses documented. Arterial doppler (Bidop®) and the ankle/brachial index (ABPI) were measured. Vibration perception threshold (VPT) measurements were performed using a hand-held biothesiometer (Biomedical Instrument, Newbury, OH, USA) at the great toes and the average of three readings on each limb were recorded. A single fasting blood sample was drawn for measurement of HbA1c, serum total cholesterol (TC), triglycerides (TG), lipid sub-fractions (HDL cholesterol (HDL) and calculated LDL cholesterol (LDL)) and serum creatinine. All collected data were entered on the PROTON database.

Additionally, hospital notes, available post-mortem reports and the primary care databases/clinical notes were searched for relevant information regarding

cardiovascular outcomes. Prescribing information pertaining to aspirin, anti-hypertensive, lipid-lowering and glycaemic-lowering therapy was collected from the primary care computer systems and the records for cohort members on PROTON were updated.

Mortality Data

Mortality data was recorded from bi-monthly reports from the ONS. International Classification of Diseases (ICD) codes were entered on a specific screen created on PROTON for both cases and controls. During the course of the study, the ONS reporting switched from ICD-9 codes to ICD-10 codes and the mortality data was recoded as ICD-10 for the later analyses.

Biochemical Analysis

All biochemical studies were performed in the biochemical laboratory at Poole General Hospital. HbA_{1c} was measured using HPLC. The HbA_{1c} measurement was DCCT-aligned using a laboratory-evolved correction factor (HbA_{1c} [DCCT] = HbA_{1c} [Poole] x 0.97]. Fasting serum total cholesterol (TC) and HDL cholesterol (HDLc), and triglycerides (TG) were measured at baseline using enzymatic methods and LDL cholesterol (LDLc) was calculated using Friedwald's equation when triglycerides were less than 4.5mmol/l. Serum creatinine was measured using a modified Jaffe method. Jo Begley organised the storage and analysis of samples for the study.

Data Storage and Statistical Analysis

Data was initially collected on PROTON and then anonymised data was exported to EXCEL (Microsoft Corp ®) as comma-separated (.csv) files. The EXCEL files were imported on to an SPSS (SPSS inc ®) database for analysis.

Initially, SPSS 10 was used for the incidence analysis. Later on in the study, analysis was performed using SPSS 12.0 and SPSS 14.0. Datasets were held at the Health Care Research Unit at Southampton General Hospital.

Descriptions of relevant patient selection, characteristics, study methods and statistical methods are detailed in subsequent chapters.

The East Dorset Local Research Ethics Committee (LREC) approved the study protocol for each of the analyses and informed consent was given by the study participants.

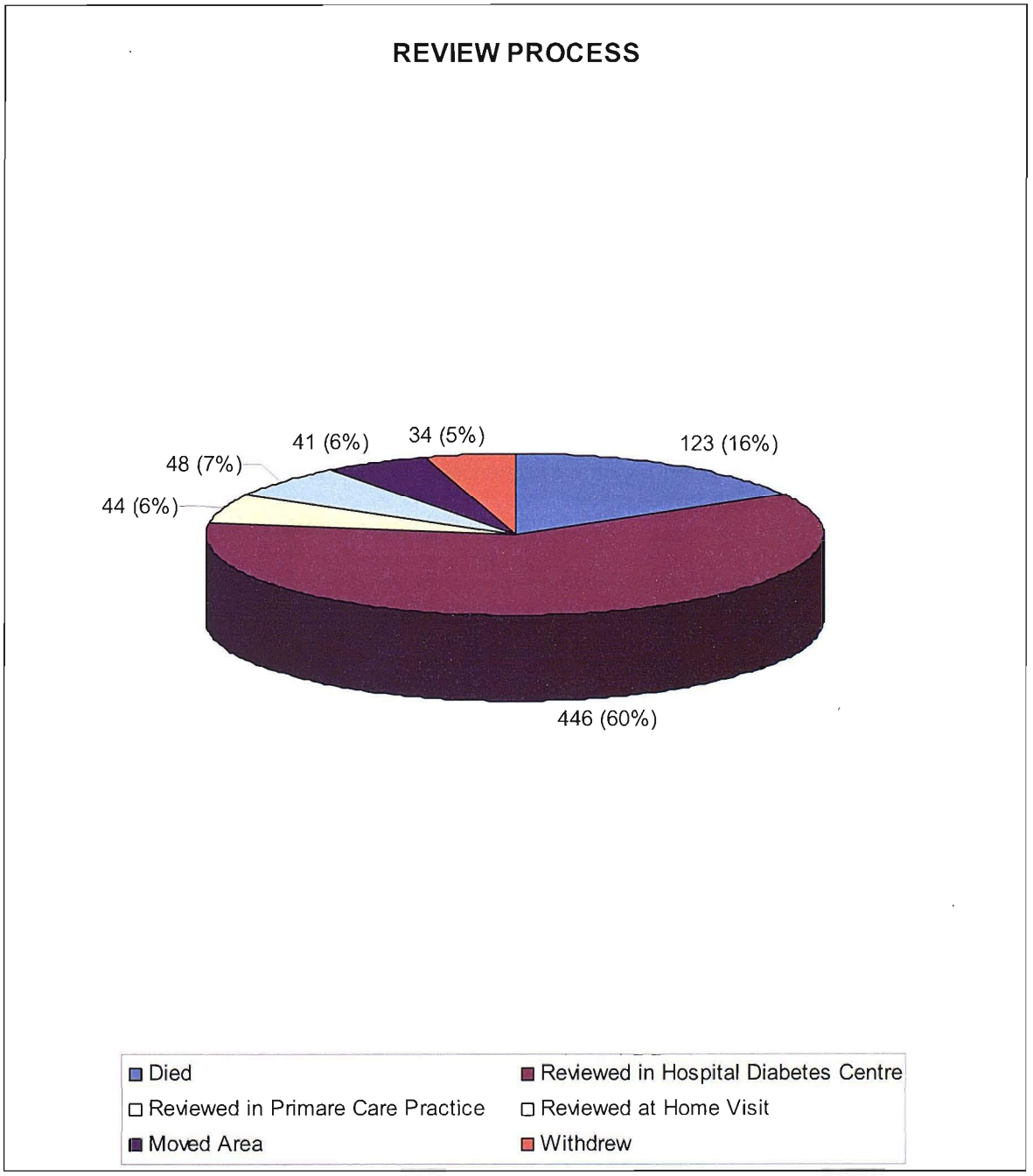


Fig. 2.1 Review Process - July 2001

Table 2.1 Definition of cardiovascular end-points used in the study protocol.

Coronary Heart Disease

Myocardial Infarction: in-patient diagnosis on hospital discharge summary or ICD-9 code (410) on death certificate or post-mortem evidence

Angina: hospital admission with unstable angina or symptoms + positive treadmill test or symptoms + abnormal coronary angiography

Cerebrovascular Disease

Stroke: in-patient diagnosis on hospital discharge summary + persistent neurological deficit or persistent neurological deficit + positive brain imaging

Transient Ischaemic Attack: in-patient diagnosis on hospital discharge summary + motor weakness resolving within 24 hours or episodic, altered level of consciousness + CT evidence of ischaemia

Heart Failure

in- patient diagnosis on hospital discharge summary or symptoms + decreased left ventricular function on echocardiography or symptoms + evidence of pulmonary congestion on chest x-ray

Peripheral Vascular Disease

claudication pain or ulceration or absent foot pulses + either

ankle/brachial pulse index ≤ 0.5 or monophasic waveform on pulse wave doppler

CHAPTER 3

Incidence of diagnosed type 2 diabetes in a geographically -defined community

Introduction

As seen in the UK Prospective Diabetes Study [32,33] (which also provided a clear vision for modern diabetes management), type 2 diabetes mellitus leads to considerable morbidity and mortality. Consequently, accurate information about the number of newly diagnosed cases and prevalence of diagnosed diabetes in the community is likely to be useful for health care planning.

It is surprising that little information is available about the number of new cases of type 2 diabetes diagnosed in the United Kingdom. The prevalence of diagnosed diabetes is increasing [2,34], mainly due to type 2 diabetes, although the reason remains unknown. This could be due to an increasing incidence of type 2 diabetes.

In this chapter, we report the number of newly diagnosed cases of type 2 diabetes found over 24 months of the study and extrapolate these findings to provide annual incidence figures for the UK.

The term "incidence" when applied to type 2 diabetes in this study refers to the frequency of newly diagnosed cases, and not to new onset of disease. Hence, the aim of this study is to establish how many new cases of type 2 diabetes are identified each year through normal health care processes in a geographically-defined population.

Study Methods

Incidence of cases of newly diagnosed type 2 diabetes was calculated from the first 24 months (1st May 1996 to 30th April 1998) of the study. Individuals diagnosed in the 25th and 26th month of the study were not included in the incidence calculations to minimise underascertainment in the closing phase of the study. It was felt that people diagnosed with diabetes around the last month could be missed if their referral was delayed. The value of this approach was evaluated by searching the hospital diabetes register for missed cases once the study period was over.

Since the age and sex distribution of the background population in the Poole study differs from that of England and Wales (for example, in the study population, 26.3% of the people were aged $\geq$ 60 years compared to 20.4% in England and Wales [35]), age and sex - standardised incidence rates of type 2 diabetes for England and Wales were extrapolated from our results using the 1997 mid year (mid-point of study) estimates of age and sex from the UK census data [35].

Results

Updating the hospital and practice registers at the start of the study identified 3,627 (1.97%) patients diagnosed with diabetes in the 24 practices leaving 181,174 (98.03%) people at risk of developing diabetes. In the first year, the surveillance programme had identified 365 new cases; 204 men and 161 women. Following the register update and the addition of an extra practice, there were 182,634 "at-risk" people for the latter 12 months of the study and 341 people; 178 males and 163 females were identified. The prevalence of diabetes (type1 and type 2) in the study population showed an increase from 1.96% (95%CI 1.90-2.03) to 2.28% (95%CI 2.21-2.34) in the two years of the study. The 1996 prevalence of diagnosed type 2 diabetes was 1.59% (95%CI 1.53-1.65) with 2941 identified cases [28].

The surveillance programme identified 659 cases and 47 were found through the register updating process. In the last two months of the study, 42 new cases of type 2 diabetes were identified. A search of the hospital diabetes register after the study had closed showed that 9 of these individuals (3 in month 25 and 6 in month 26) would have been among those missed, due to late referral, if the entire 26-month period had been utilised.

In the study population, the crude annual incidence of newly diagnosed type 2 diabetes was 1.93 per 1000 (95% CI 1.73 - 2.13). With age/sex adjustment for England and Wales, the annual incidence fell to 1.67 per 1000 (95% CI 1.49 - 1.84) (**Table 3.1**). The age-adjusted incidence in men, 1.86 per 1000 (95% CI 1.60 - 2.13) was higher than in women, 1.48 per 1000 (95% CI 1.25 - 1.71) but this was not statistically significant.

The mean age at presentation was 64.3 years (range 19-96 years). Mean age for men, 62.9 (SD 12.3) and for women, 65.9 (SD 14.3), women being significantly older at the time of diagnosis ($t=3.2$, $p<0.01$, 95% CI for difference in means = 1.16, 4.98). Incidence peaked after the age of 60 in both sexes (**Fig. 3.1**). Fifty-one per cent of the patients were aged over 65 years at diagnosis.

Using the number of new cases of type 2 diabetes diagnosed in the Poole Diabetes Study during one year, it is possible to extrapolate these rates, after age and sex adjustment, to England and Wales, as a whole. Based on the 1997 mid -year population estimates we estimate that over 98,000 people have type 2 diabetes diagnosed each year in England and Wales.

Table 3.1 The crude and age adjusted incidence of type 2 diabetes mellitus.

	All	Males (m)	Females (f)	P value (m vs. f)
Cases (n)	706	382	324	
Crude incidence/1000 (95%CI)	1.93 (1.73 - 2.03)	2.17 (1.86 - 2.48)	1.71 (1.45 - 1.99)	
Age/sex adjusted incidence/1000 (95%CI)	1.63 (1.49 - 1.84)	1.86 (1.60 - 2.13)	1.48 (1.25 - 1.71)	
Mean age at diagnosis (±SD)	64.3 (±13.2)	62.9 (±12.3)	65.9 (±14.3)	0.002

*Adjustment for age and sex distribution of the UK, OPCS 1997 [35]

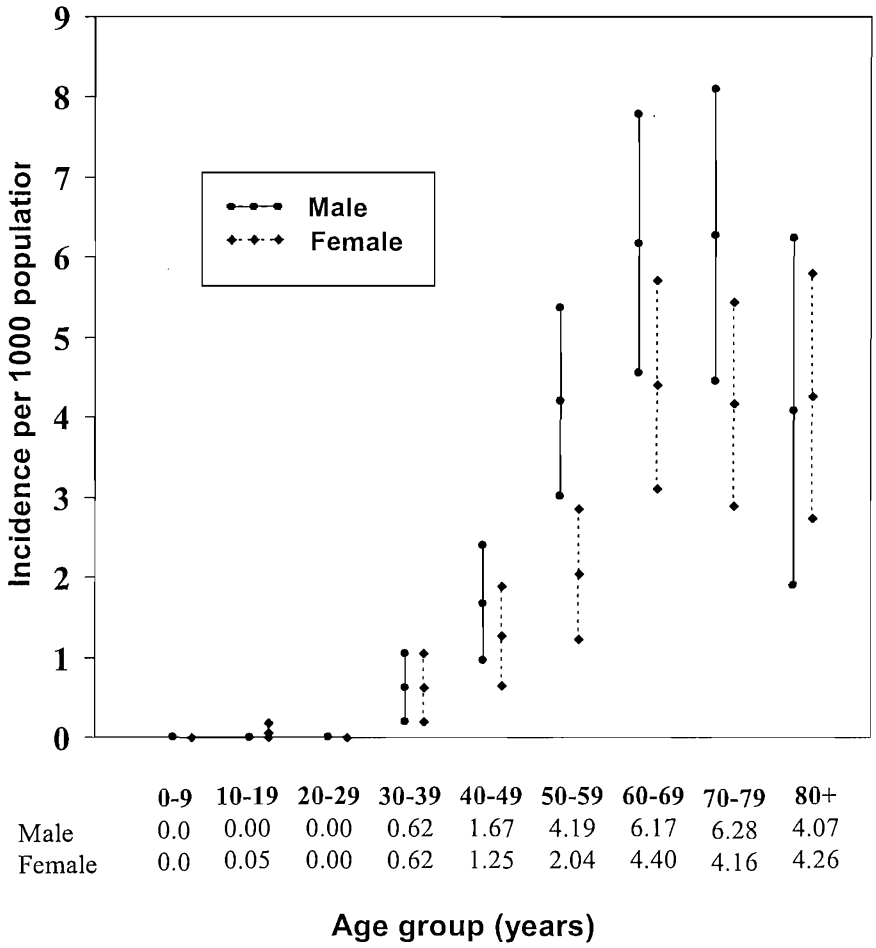


Fig 3.1 Incidence of newly diagnosed Type 2 diabetes by age and sex

Discussion

We report the number of cases of type 2 diabetes mellitus diagnosed in the community through the normal health care processes. Underascertainment of cases should have been minimal as the surveillance programme included both primary and secondary care and collation of patient data from multiple registers.

Although the "capture-recapture" method has been cited as a valuable method of establishing the prevalence and incidence of type 2 diabetes [36], its use in this study is limited, as inter-dependence of lists of patients with newly diagnosed diabetes causes overestimation of the completeness of ascertainment. In the Poole area, this dependence between hospital and community diabetes records is high. The Poole Diabetes service involves the referral of the majority of newly diagnosed patients to the hospital education sessions, and thus inclusion on the hospital diabetes register [37].

Establishing the true incidence of type 2 diabetes would involve regular screening of a stable population since it is recognised that there are many undiagnosed cases in the community. In the Ely study [38], screening people aged 40 to 65 years identified 4.5% of the population who had previously unrecognised diabetes. However, within the NHS, there is no regular population screening for diabetes so such a study would not reflect the normal health care processes in the UK. The Poole Diabetes Study was established to reflect current medical practice.

Defining an accurate denominator population is important for any epidemiological study. Using people registered with primary health care services

is a well-recognised method. However, inaccuracies in the list size can occur due to failure of notifications, death, people moving away and people failing to register. Conversely, people with diabetes are more likely to register with primary care to receive regular prescriptions. It is probable that these effects are relatively small but are recognised weaknesses of primary care studies.

There are no directly comparable published studies in the UK. A study in Wessex [39] of patient empowerment in newly diagnosed patients with diabetes found a crude incidence of 1.16 per 1000. The Whickham study [40] used a different methodology, initially screening the population and then retrospectively identifying new cases after 20 years. In this small population of 2779 adults, the total incidence was 2.2 per 1000 but this included cases identified through initial screening. However, the incidence in the survivors, 1.7 per 1000 (95% CI 1.3-2.2), was comparable to the Poole Study. In comparison, despite a narrower age group, the Reykjavik study [41] reported a much higher incidence of type 2 diabetes in Iceland than found in Poole; 3.8 for men and 2.7 for women aged 35 to 74 years.

A higher incidence of newly diagnosed type 2 diabetes in men than women was consistent in all 3 studies though the rates in the Whickham study [40] were more comparable to Poole; 2.1 per 1000 in men and 1.6 in women. Surveys in other countries including Sweden [42] and USA [43] have reported a similar and non-significant sex difference. Population screening shows a similar prevalence of undiagnosed diabetes in men and women [44].

There does not appear to be a clear explanation for the difference in mean age at diagnosis for men and women. It is possible that men are less tolerant of

polyuria due to concurrent prostatic enlargement after 50 years of age and present with symptoms earlier to their practitioners.

The surprisingly high level of HbA_{1c}, mean 10.8%, emphasises the delay in diagnosis in many patients and may explain the common finding of microvascular complications at presentation of type 2 diabetes. The UKPDS [32,33] reported that intensive treatment of both blood pressure and glucose levels reduced the long-term development of complications. This provides a clear guide for our management principles but to have a real impact on the natural history of the disease, earlier diagnosis is imperative. The development of an effective national screening programme, which is presently being debated by the National Screening Committee, would address this issue. The mean HbA_{1c} at diagnosis in this study was considerably higher than the mean, 7.0 to 7.9%, seen in both treatment arms of the UKPDS [32].

Screening population studies [40,44] show an increasing prevalence of diabetes with age but we have found the highest incidence of newly diagnosed type 2 diabetes was not in the oldest age group. The overlap of symptoms such as lethargy with features of ageing may mask the need for investigation and leave a larger proportion of patients undiagnosed in the more elderly population. Further investigation into understanding why people present with symptoms at any particular time or age, may help to develop strategies for earlier diagnosis.

The overall prevalence of diabetes in this population is increasing as demonstrated in an earlier paper from Poole [2]. We were unable to show a significant change in the incidence of diagnosed diabetes between 1996 and 1998 to account for the changing prevalence. It is possible that the increasing

prevalence could be attributed to net migration, as the area has an elderly population with a steady influx of retirees, along with improved survival. This finding will need further investigation.

The Poole population is mainly Caucasian with only a tiny ethnic minority and so, extrapolations to the UK will tend to underestimate the rate in groups, such as Asians, known for their higher prevalence of diabetes. [44,45]. Allowing for this, the number of newly diagnosed patients with diabetes in the UK is large and demands the allocation of adequate health care resources.

CHAPTER 4

Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed type 2 diabetes

Introduction

In the United Kingdom, guidelines for primary prevention of cardiovascular disease (CVD) require multi-factorial risk assessment prior to considering lipid-lowering therapy. The National Institute of Clinical Excellence (NICE) guidance [5] issued in late 2002 (and supported by the National Service Framework (NSF) for diabetes [46] lowered the threshold for pharmacological intervention to a calculated 10-year coronary heart disease (CHD) risk level of 15% in people with diabetes as opposed to the 30% 10-year CHD risk level applied in the general population. NICE recommended intervention in those individuals with total cholesterol greater than 5 mmol/l.

The NSF for CHD [22] and the Joint British Guidelines [21] recommended use of the Framingham risk function [20] to assess risk. In the absence of prospective validation studies, it is uncertain whether the Framingham algorithm accurately predicts the risk of CHD in people with diabetes in the UK population [47,48].

In 2001, the UKPDS risk engine for CHD [23] was published offering the inclusion of more diabetes-specific variables like duration of diabetes and glycaemic control.

However, in the United States, the ADA (American Diabetes Association) and the NCEP-ATPIII (National Cholesterol Education Program Expert panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)) guidelines adopted lipid thresholds (LDL cholesterol (LDLc) ≥2.6 mmol/l or triglycerides ≥4.5 mmol/l) used for secondary prevention of coronary heart disease (CHD) to identify individuals with type 2 diabetes who should receive lipid-lowering therapy [24,49].

This study was designed to investigate whether the Framingham risk function reliably predicts the risk of cardiovascular disease in patients with newly diagnosed type 2 diabetes, a finding that would support its use as a decision-making tool. Since the UKPDS risk engine was published during the course of the study, we have investigated its prognostic value, as well. Additionally, we compared the sensitivities and specificities of approaches based on a 15%, 10-year CHD risk threshold using both risk engines (with and without the present total cholesterol intervention level of > 5mmol/l) and that based on a lipid risk-factor threshold (LDLc ≥ 2.6 mmol/l or triglycerides ≥ 4.5mmol/l) in identifying individuals who develop clinically evident cardiovascular disease in the initial years after diagnosis of type 2 diabetes.

Study Methods

Study Participants

Of the 736 cohort members, those aged less than 30 years or 75 years and over at the time of diagnosis were excluded from the data analysis to comply with the limitations of the Framingham risk function [20,50]. Individuals with pre-existing cardiovascular disease were also excluded.

Fig. 4.1 details the recruitment process for the study. In all, 455 individuals (259 males, 196 females) entered the prospective phase of the study.

Design

Pre-existing illness was defined as self-reported cardiovascular disease, evidence of a cardiovascular illness during the note review process and/or interview, or the presence of probable myocardial infarction on the ECG based on the Minnesota code. The mean follow-up in the study was 4.2 (SD ±0.6) years. Predicted CVD and CHD risk scores for each individual from the time of their entry to the close of the study were calculated from the Framingham risk function [20] and CHD risk scores only from the UKPDS risk engine [23] as it is CHD-specific. Risk scores were derived for each end-point both with and without the inclusion of electrocardiographic left ventricular hypertrophy (LVH) as a covariate in the equation. Ten-year primary CHD risk scores were calculated to summarise the distribution of risk profiles in the study population.

Coronary and cardiovascular mortality and morbidity during the study was determined in participants. Primary cardiovascular and primary coronary events were recorded separately, and subsequent events were excluded from the data

analysis. **Table 2.1** describes the pre-defined end-points used to identify cardiovascular events.

Statistical Analysis

The prognostic value of the Framingham risk function and UKPDS risk engine were evaluated in terms of discrimination, calibration, sensitivity and specificity.

Discrimination Discrimination is a measure of the probability that a model assigns a higher risk to those who go on to have an event than to those who do not. A value of 0.5 (50%) indicates a test with a complete lack of discrimination (equivalent to a coin-toss) and a value of 1.0 indicates a test with perfect (100%) discriminative ability. Discrimination was quantified by calculating the *c* statistic (with 95%CI). This involves plotting a receiver operating characteristic (ROC) [51] curve (false positive rate on the x-axis and sensitivity on the y-axis for all available test values) and calculating the area under the curve (AUC). **See Appendix A**

Calibration Calibration is a measure of the "goodness of fit" of a test determining how closely predicted outcomes agree with actual outcomes. The modified Hosmer-Lemeshow x^2 statistic [52,53], which divides the cohort into deciles of calculated risk and compares this with actual outcomes in each decile was used. Small values (less than 15) indicate good calibration, and values exceeding 20 indicate a distinct lack of calibration ($p<0.01$). **See Appendix B**

Sensitivity Sensitivity is the percentage of all patients with disease present who have a positive test.

Specificity Specificity is the percentage of all patients without disease who have a negative test.

The discriminative ability of the risk function was studied in pre-defined patient groups based on gender and pre-treatment with anti-hypertensive therapy to evaluate the consistency of results seen in the primary analysis. The limited study size precluded analysis of calibration in these sub-groups.

The sensitivity and specificity of the Framingham equation and UKPDS Risk Engine for primary CVD at the 15% 10-year CHD risk threshold (with and without the present total cholesterol intervention level of > 5mmol/l) were compared with that of the American Diabetes Association's lipid intervention threshold of an LDLc ≥ 2.6 mmol/l or triglycerides ≥ 4.5mmol using McNemar's test. The now outmoded 30% 10-year threshold was also tested to evaluate the impact of the recent reduction in treatment threshold.

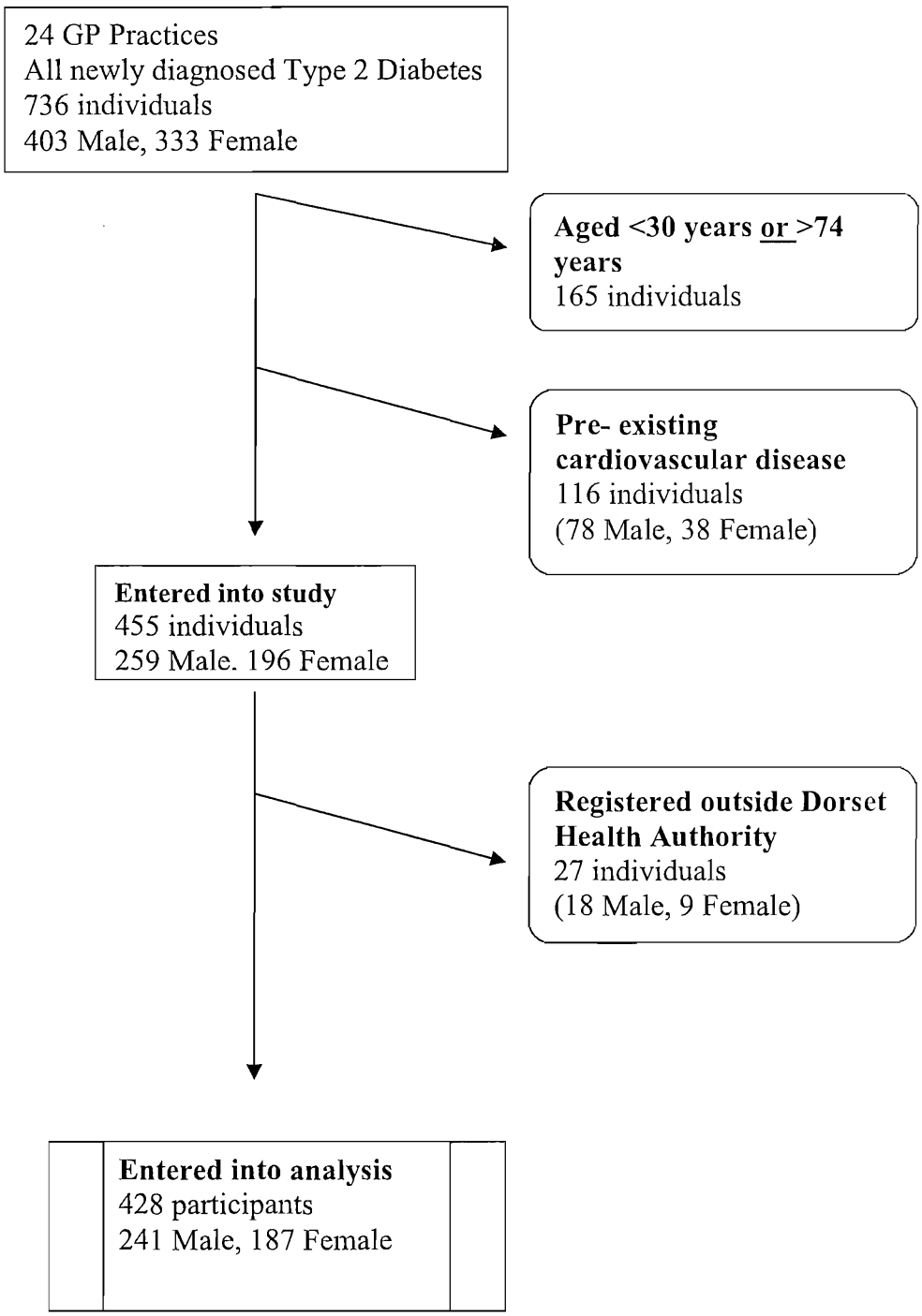


Fig. 4.1 Recruitment of the study population

Results

Twenty-seven members (18 male and 9 female) of the original cohort registered outside the Dorset Health Authority during the course of the study. Their cardiovascular status was unknown and we excluded them from the analysis. **Table 4.1** describes the baseline characteristics of the remaining 428 participants (241 males and 187 females, comprising 94% of the original cohort). **Fig. 4.2** details the distribution of predicted 10-year CHD scores. Using both risk calculation methods, similar proportions were assigned 10-year risk scores less than 15% (27.3% and 25.7%). However, the UKPDS risk engine assigned a ten-year score over 30% to 187 (43.7%) of the study participants as compared to only 88 (20.5%) when derived from Framingham.

Forty (9.3%) participants died during the course of the study. The death certificate recorded cardiovascular disease as the underlying cause in 18 (45%) of these individuals. Ninety-eight primary cardiovascular events were identified during the course of the study. Of these, 37 were episodes of angina/unstable angina, 11 were fatal and non-fatal MI, 21 were cerebrovascular disease (strokes 9, TIAs 12), 17 were cases of peripheral vascular disease, and 12 were of heart failure. Recording only primary CHD events, 60 such episodes were identified (47 new diagnoses of stable/unstable angina and 13 of fatal/non-fatal myocardial infarction). Participants suffering a non-CHD (as defined in the study protocol) cardiovascular event followed by a primary CHD event explain the difference in the number of angina and MI events in the CVD and CHD arms as these two study end-points were analysed independently.

When the study closed on 31st July 2001, 102 (24%) participants were receiving low-dose aspirin, 244 (57%) were on anti-hypertensive medication, and 113 (26%) on lipid-lowering agents. The participants who developed clinically evident cardiovascular disease during the course of the study accounted for 65 (64%) of the aspirin prescriptions, 85 (35%) of those on anti-hypertensive therapy, and 61 (54%) of the prescriptions for a lipid-lowering agent.

At the level of the entire cohort, the number of events predicted by the Framingham risk function underestimates both true CVD and CHD events by 33% and 32%, respectively as opposed to the statistically non-significant 13% of CHD events in the case of the UKPDS risk engine. The Framingham results suggest a tendency towards a greater degree of underestimation of CHD events in men than in women (41% vs. 26%) and for pre-treated blood pressure rather than untreated measurements (42% vs. 31%). The UKPDS risk engine confirms the trend in relation to anti-hypertensive therapy (21% vs. 8%) but differs in relation to gender (men - 16% vs. women - 10%). However, in relation to prognostic value on an individual basis, both risk assessment methods show moderate discrimination and poor calibration. The secondary analyses and specifically those relating to pre-treatment with anti-hypertensives and to gender show similar discrimination. The exclusion of LVH does not have a detrimental effect on the discrimination measurement. The results of the discrimination and calibration analyses are summarised in **Table 4.2a** and **Table 4.2b** for the Framingham and UKPDS risk equations, respectively.

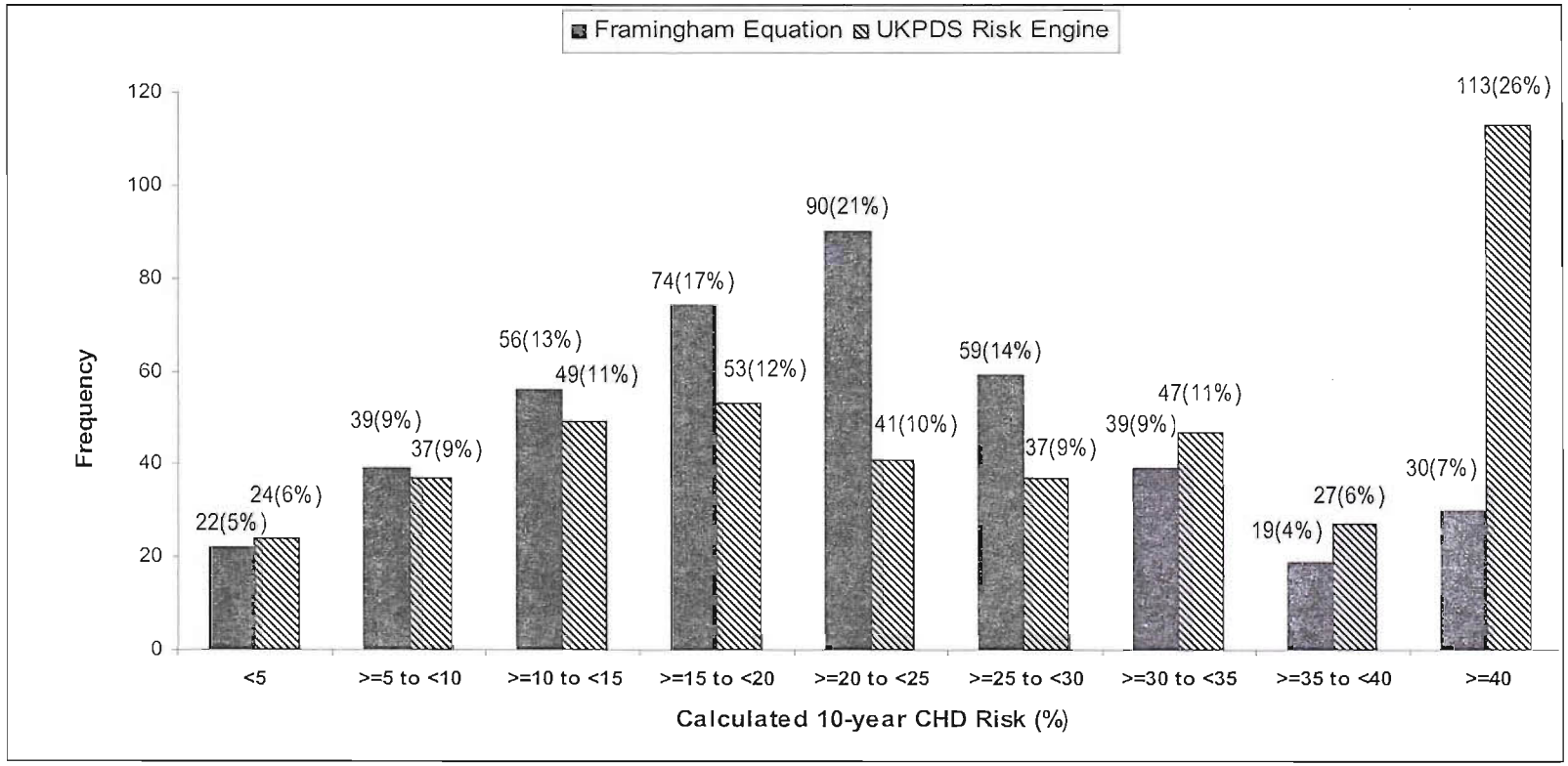
The results of the sensitivity and specificity analyses are summarised in **Table 4.3.** The sensitivity of the 15% 10-year CHD and TC > 5 mmol/l threshold

for primary cardiovascular disease using both risk assessment methods was poorer than that of the LDLc ≥ 2.6 mmol/l or TG ≥ 4.5 mmol/l but more specific. The 15% 10-year CHD risk threshold, by itself, had a similar sensitivity and better specificity.

Table 4.1 Baseline characteristics of the 428 study participants.

Age (years)	58.6 (±11.1)
Males	241 (56%)
Females	187 (44%)
Systolic Blood Pressure (mmHg)	142 (±21.4)
Diastolic Blood Pressure (mmHg)	81 (±12.1)
Total cholesterol (mmol/l)	5.9 (±1.1)
Triglycerides (mmol/l)	2.0 (1.48-2.8)*
HDL cholesterol (mmol/l)	1.11 (0.93-1.30)*
LDL cholesterol (mmol/l)	3.6 (±0.9) †
TC: HDLc ratio	5.4 (±1.6)
HbA_{1C} at diagnosis (%)	10.3 (8.0-12.1)*
BMI at diagnosis (kg/m^2)	31.5 (±7)
Active Smokers	100 (23%)
Anti-hypertensives at diagnosis	136 (32%)
Lipid-lowering therapy	5 (1%)
Anti-platelet therapy	12 (3%)
LVH on ECG	22 (5.5%)

Mean (±Standard Deviation) or n(%)
*Median (inter-quartile range)
† n=388 as 40 participants had serum triglyceride levels greater than 4.5mmol



n=428. Percentages rounded to whole numbers

Fig. 4.2 Distribution of calculated 10-year CHD risk (%) based on the Framingham and UKPDS risk functions.

Table 4.2a Comparison of the proportions of actual and predicted cardiovascular and coronary heart disease events using the Framingham model.

		Cardiovascular Disease (CVD)					Coronary Heart Disease (CHD)				
	n	Actual events [A] (%; 95%CI)	Predicted [P] (%)	Ratio P/A	Discrimination c statistic (95%CI)	Calibration HL x ^{2} (p value)	Actual events [A] (%; 95%CI)	Predicted [P] (%)	Ratio P/A	Discrimination c statistic (95%CI)	Calibration HL x ^{2} (p value)
All cohort members	428	98 (22.9; 19.2-27.1)	66 (15.4)	0.67	0.673 (0.612-0.734)	32.8 (p<0.001)	60 (14.0; 11.0-17.6)	41 (9.6)	0.68	0.657 (0.581-0.732)	19.8 (p=0.011)
All cohort members (excluding LVH)	428	98 (22.9; 19.2-27.1)	65 (15.2)	0.66	0.678 (0.618-0.739)	39.5 (p<0.001)	60 (14.0; 11.0-17.6)	40 (9.2)	0.67	0.665 (0.591-0.740)	22.6 (p=0.004)
Males	241	63 (26.1; 21.0-32.0)	41 (16.9)	0.65	0.669 (0.590-0.747)	*	41 (17.0; 12.8-22.2)	24 (10.1)	0.59	0.726 (0.643-0.810)	*
Females	187	35 (18.7; 13.8-24.9)	25 (13.2)	0.71	0.678 (0.580-0.776)	*	19 (10.2; 6.6-15.3)	14 (7.6)	0.74	0.697 (0.635-0.760)	*
Pre-treated blood pressure	136	40 (29.4; 22.4-37.6)	24 (17.3)	0.60	0.634 (0.530-0.739)	*	24 (17.6; 12.2-24.9)	14 (10.4)	0.58	0.666 (0.538-0.795)	*
Untreated blood pressure	292	58 (19.9; 15.7-24.8)	42 (14.3)	0.66	0.690 (0.613-0.767)	*	36 (12.3; 9.0-16.6)	25 (8.7)	0.69	0.663 (0.568-0.758)	*

*Not calculated due to insufficient cohort members/predicted events.
Percentages rounded to one decimal place; predicted events to whole numbers.

Table 4.2b Comparison of the proportions of actual and predicted coronary heart disease events using the UKPDS Risk Engine.

		Coronary Heart Disease (CHD)				
	n	Actual events [A] (%; 95%CI)	Predicted [P] (%)	Ratio P/A	Discrimination c statistic (95%CI)	Calibration HL x^2 (p value)
All cohort members	428	60 (14.0; 11.0-17.6)	52 (12.1)	0.87	0.670 (0.598-0.742)	17.1 (p=0.029)
Males	241	41 (17.0; 12.8-22.2)	37 (15.4)	0.90	0.673 (0.585-0.761)	*
Females	187	19 (10.2; 6.6-15.3)	16 (8.6)	0.84	0.618 (0.491-0.746)	*
Pre-treated blood pressure	136	24 (17.6; 12.2-24.9)	19 (14.0)	0.79	0.696 (0.575-0.817)	*
Untreated blood pressure	292	36 (12.3; 9.0-16.6)	33 (11.3)	0.92	0.648 (0.559-0.736)	*

*Not calculated due to insufficient cohort members/predicted events.
Percentages rounded to one decimal place; predicted events to whole numbers.

Table 4.3 Sensitivities and specificities for cardiovascular disease of approaches based on multifactorial risk assessment and lipid risk factor thresholds.

	Sensitivity % (95% CI; p)	Specificity % (95%CI; p)
30% 10-year CHD risk and TC > 5mmol/l		
Framingham Model	29.6 (22.2 - 37.2; <0.001)	88.5 (86.3 - 90.7; <0.001)
UKPDS Risk Engine	50.0 (39.7 - 60.3; <0.001)	69.1 (63.8 - 74.0; <0.001)
15% 10-year CHD risk and TC > 5mmol/l		
Framingham Model	72.4 (63.5 - 80.2; <0.001)	45.2 (42.5 - 47.5; <0.001)
UKPDS Risk Engine	76.5 (66.9 - 84.5; <0.001)	46.4 (40.9 - 51.9; <0.001)
15% 10-year CHD risk only		
Framingham Model	85.7 (77.8 - 91.5; 0.21)	33.0 (30.7 - 34.7; <0.001)
UKPDS Risk Engine	89.8 (82.0 - 95.0; 0.34)	30.3 (25.4 - 35.6; <0.001)
LDLc ≥ 2.6 mmol/l or TG ≥ 4.5 mmol/l	93.9 (87.8 - 97.4)	12.1 (10.3 - 13.2)

CHD = coronary heart disease, TC = total cholesterol, LDLc = LDL cholesterol, TG = Triglycerides
Significance (p) versus last row (LDLc≥2.6 mmol/l or TG≥4.5mmol/l)

Discussion

This study demonstrates that in newly diagnosed diabetes, both the Framingham risk equation and the UKPDS risk engine have modest discrimination and are poorly calibrated. In spite of these limitations, a threshold of 15% 10-year CHD risk, on its own, is a more effective tool in identifying people that develop clinically evident vascular disease early after diagnosis of type 2 diabetes than the NCEP-ATPIII lipid thresholds. We feel these are important concepts given the results of the Heart Protection Study (HPS) that showed sustained benefits in terms of risk reduction even in individuals with levels of LDLc less than 3mmol/l at the time of study entry [54]. The authors suggest that statin therapy should now be considered routinely for all diabetic patients at sufficiently high risk of major vascular events, irrespective of their initial cholesterol concentrations.

If the present cholesterol targets were lowered to the cut-off levels used in the HPS, virtually the entire population with type 2 diabetes in western countries would be eligible for statin therapy. This has given impetus to the idea that all patients with type 2 diabetes should receive a statin. The economic implications of such an approach for a cash-strapped health system like the NHS are enormous. Present guidelines aim to target those individuals at risk of developing clinical atheromatous disease. If effective, these strategies reduce unnecessary exposure to drugs and polypharmacy in the remainder of the diabetic population and maximises cost-effectiveness. Furthermore, an accurate measure of absolute risk may help inform the aggressiveness of therapy aimed at lowering risk in an individual and aid in patient education.

The belief that diabetes is a CHD risk-equivalent is based on a Finnish study by Haffner published in 1998 [55]. However, a recent observational study from Tayside, Scotland failed to confirm the observation [56]. Differences in study design may partly explain this discrepancy. The Finnish study excluded diet-treated patients who may have been at a lower risk. In the Scottish study, the non-diabetic participants in the cross-sectional study had a mean time since myocardial infarction (MI) of 3.5 years. The cohort study, reported in the same paper, showed a relative clustering of events seen in the MI group in the first three years following the MI. Beyond this, the event rates in the diabetic and non-diabetic groups appeared to approximate. It is likely that the Finnish study recruited individuals with a longer duration following their myocardial infarction. There is little doubt that both men and women with type 2 diabetes are at high-risk of CHD as seen in the Atherosclerosis Risk in Communities Study (ARIC) study [57]. Nonetheless, the results of the Tayside study suggest that even among people with type 2 diabetes, attempting to identify individuals at particularly high-risk of developing vascular disease is clinically relevant.

Cardiovascular disease being the main cause of death and a significant cause of morbidity in type 2 diabetes, the strategies adopted to reduce this burden assume great importance. It has been argued that when considering a therapeutic intervention aimed at primary prevention of CVD, knowledge of the absolute level of risk for an individual patient is more important than the level of individual physiological variables. Treatment decisions based on individual risk factor thresholds ignore the impact of age, which is the most important determinant of primary cardiovascular disease. People of a given age with relatively high levels of other risk factors are at similar risk as people a few

years older with average levels of these risk factors. The benefit of therapeutic intervention would be just as effective in reducing events in either group. Multi-factorial cardiovascular risk assessment is likely to be more useful in identifying the subset of patients with type 2 diabetes who would most benefit from intervention, namely those above a defined absolute risk threshold.

European [58] and United Kingdom [21,22] primary prevention guidelines propose the identification of individuals with a calculated risk above a pre-defined threshold using multifactorial risk assessment techniques prior to introducing lipid-lowering therapy. The Framingham cardiovascular risk function, which is widely employed to estimate CVD and CHD risk, is a survival model based on the Weibull distribution and derived from the risk profiles of 5573 CHD-free members of the Framingham cohort, aged 30 to 74 years and followed for 12 years [20,50], 6% of whom had diabetes [59]. The New Zealand charts [60], Sheffield Risk Tables [61], and the Joint British Guidelines charts [21] make use of modified versions of the Framingham model. A casual plasma glucose levels greater than 8.3mmol/l (in the offspring cohort, a fasting plasma glucose of 7.8mmol/l) and a history of oral hypoglycaemic or insulin therapy identified participants with diabetes in the Framingham cohort. The Framingham population did not consist of patients with newly diagnosed diabetes, an aspect of the study design that could have introduced a "survivor effect". The equation did not include proteinuria and microalbuminuria, both strong predictors of cardiovascular risk in type 2 diabetes. It is possible that the diabetic cohort in Framingham may have been more physically active and had a lesser degree of central adiposity than people with diabetes diagnosed in the last decade. This last assumption, if true, would explain the relative lack of improvement in historic CHD mortality

trends in the diabetic population. These factors, when taken together, suggest that the Framingham risk function may fail to predict accurately the risk of CVD and CHD in the presence of diabetes.

The UKPDS Risk Engine [23] for determining CHD risk is derived from participants in the UKPDS study. It includes diabetes-specific covariates in the form of glycaemic control (HbA_{1c}) and duration of diabetes.

We are not aware of any published study that has assessed the validity of either the Framingham risk function or the UKPDS Risk Engine in a population with newly diagnosed diabetes. Framingham coronary heart disease prediction scores have recently been validated in non-diabetic cohorts of different ethnic origin [62]. Though they applied to white people and African Americans, they needed recalibration in other ethnic groups (Japanese, Hispanic, and native Americans). In Southern European populations with a lower rate of CHD, the Framingham equations overestimate risk [63]. The Normative Aging Study reported modest discrimination in the general population with a c-statistic of 0.63 [64]. Even within the general population in the United Kingdom, there is limited and conflicting data available. A retrospective study with 1700 participants, 14 (0.8%) of whom had diabetes, found that the Framingham model reliably predicted the absolute risk of heart disease in white men and women when the annual risk of CHD is above 1.5% per annum [65]. However, a recent study in British men concluded that current risk scoring methods derived from the Framingham model significantly overestimated absolute coronary risk [66].

What this study adds

We have studied all patients with newly diagnosed diabetes in a defined community. The results reflect usual clinical practice in both the hospital and

primary care setting. Some limitations associated with the study design may have led to a reduction in the difference between actual and predicted risk and it is possible that the risk functions underestimate cardiovascular risk by an even greater degree than seen in the study. First, we did not include sub-clinical CHD events and silent ischaemia in the study. Second, the population studied resides in a relatively affluent, predominantly white area of the United Kingdom. The results may not be applicable to inner-city populations with high levels of deprivation or in those with a large South Asian presence. Third, the treatment changes seen during the study are likely to have influenced the results. A large proportion of the therapeutic interventions relate to secondary prevention. However, the remaining primary interventions will have influenced the true risk of cardiovascular disease in this group of individuals. The average follow-up period in the study was 4.2 years. Over a ten-year period, it is conceivable that the results will change, though the year on year statistically non-significant small increase in cardiovascular event rates seen in the study make this unlikely and the study duration is comparable to primary lipid-lowering intervention trials [54,67] indicating that the findings are clinically relevant. The size of the study precludes us from drawing firm conclusions from the population sub-sets. For instance, it is quite likely that blood pressure measurements on treatment will introduce an underestimate in the risk function, as the true risk is likely to reflect a level between the measured blood pressure and the individual's habitual blood pressure prior to treatment. Our results suggest a greater underestimate in this group, but do not reach statistical significance. Nonetheless, this only applies to the application of the model to determine overall CVD or CHD rates within a population. In relation to

prognostic value for the individual (a key aspect of the clinical utility of risk calculators), the discrimination of both the UKPDS risk engine and the Framingham model is unaffected by anti-hypertensive therapy or gender. Similarly, our results would suggest that the UKPDS Risk Engine performs better than Framingham in terms of predicting overall CHD rates in the cohort and in the sub-groups. This may have implications for its adoption in research planning (eg. Determination of sample sizes) and public health related usage (eg. resource allocation). However, in relation to health outcomes for the individual participant, the performance is very similar to that of the Framingham equation.

The HbA_{1c} measurements relate to the time of diagnosis. Measurement of risk following diagnosis and a period of dietary intervention is likely to result in substantially lower calculated risk. This may explain some of the differences in risk score distribution between the Framingham and UKPDS methods demonstrated in Figure 2.

The cholesterol measurements were performed on serum and not plasma (as utilised in the original Framingham publication). Applying a correction factor of 3%-4.7% as suggested by Wickis GG et al [68] and Cloey T et al [69] do not alter our findings and only introduces a minimal increase in the underestimate shown with the Framingham equation

We have not distinguished between "hard" and "soft" CHD events as the study was designed from a pragmatic perspective to evaluate present clinical practice and the UK guidelines [21,22] do not make this distinction (the Joint British Guidelines CHD Risk charts/calculators [21] are derived from the original 1991 Framingham publication [20]).

An additional finding in this study was that the inclusion of LVH in the Framingham equation has no impact on discriminative ability and only a marginal adverse effect on calibration. In the primary care setting, an ECG may not always be available for patients with a new diagnosis of type 2 diabetes. Controversy surrounds the use of electrocardiographic criteria for left ventricular hypertrophy (ECG-LVH) in the risk equation. ECG-LVH was a covariate found in only 0.8% of participants in Framingham and with its inclusion, the 95% confidence intervals for predicted 10-year CHD risk increased considerably to ±14% [20]. The Joint British Guidelines dispense with this dichotomous variable in their published charts [21]. Our results suggest that the lack of this information need not preclude assessment of cardiovascular or coronary heart disease risk if Framingham-based assessment methods are adopted.

We hope that our results will help engender the further development of risk prediction tools specifically for diabetes. These tools may perform better if they are derived from diabetic populations and include other risk factors like body mass index, waist-to-hip ratio, lipoprotein(a), apolipoprotein B, pro-thrombotic factors, albumin, creatinine, and physical activity as shown in a recent publication by the Atherosclerosis Risk in Communities Study (ARIC) investigators (albeit, with only a small improvement in performance) [57]. Measures like microalbuminuria (integrating this with the Framingham model has been described by Yudkin et al in 1999 [70]) and proteinuria are likely to add predictive value.

In relation to lipid-lowering therapy, our results would favour either a Framingham risk equation or UKPDS risk engine derived 15% 10-year CHD risk

threshold to identify individuals with newly diagnosed diabetes requiring pharmacological intervention, when compared with an LDLc treatment threshold of 2.6mmol/l. However, restricting lipid-lowering therapy to individuals with total cholesterol levels greater than 5 mmol/l, as suggested in the present UK guidelines, results in a less effective clinical tool with regard to sensitivity and revision of this threshold needs to be debated.

CHAPTER 5

Impact of metabolic syndrome criteria on cardiovascular disease risk in people with newly diagnosed type 2 diabetes

Introduction

The metabolic syndrome, a concurrence of several cardiovascular risk factors (obesity and its central distribution, increased plasma glucose, increased plasma triglycerides, decreased HDL cholesterol and increased blood pressure) has become a subject of great interest because of its association with the development of type 2 diabetes and atherosclerotic cardiovascular disease. Two related but slightly differing definitions for the metabolic syndrome, which can be used in people with diabetes, have been formulated by expert groups: by the World Health Organization (WHO) Consultation in 1999 [71] and by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) in 2001 [24]. The European Group for Study of Insulin Resistance (EGIR) definition [72] was developed for use in people without diabetes. In 2005, the International Diabetes Federation (IDF) consensus definition [available at http://www.idf.org/webdata/docs/IDF_Metasyndrome_definition.pdf (Accessed 8th August 2005)] was released that differs from the NCEP in having lower thresholds for waist circumference and fasting glucose. In non-diabetic populations, the metabolic syndrome has been shown to be associated with an increased risk of major coronary events and cardiovascular mortality [73-77].

The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) provides a definition of the metabolic syndrome that is pragmatic, applicable to routine clinical practice and uses variables that are easily measurable. In the WOSCOPS study, modified NCEP criteria metabolic syndrome increased the risk for a CHD event and predicted CHD events in a multivariate model incorporating conventional risk factors [78]. Men with four or five features

of the syndrome had a 3.7-fold increase in risk for CHD and a 24.5-fold increase for diabetes compared with men with none.

Alexander et al. described the association between NCEP metabolic syndrome and the prevalence of coronary heart disease (CHD) using cross-sectional data drawn from participants aged over 50 years in NHANES III (National Health and Nutrition Exam Survey III) [79]. They showed that the prevalence of metabolic syndrome in diabetes was very high and that the prevalence of CHD markedly increased in the presence of the metabolic syndrome. Furthermore, the study demonstrated that participants with diabetes and without the metabolic syndrome have a similar prevalence of CHD as those with neither and participants with both diabetes and the metabolic syndrome had the highest prevalence of CHD. However, the impact of these metabolic syndrome features on cardiovascular risk in people with diabetes has not been demonstrated within the setting of a prospective study. Informative comparisons will be possible from results of studies in which both cross sectional and prospective data are available in people with diabetes.

We have investigated the association of the presence of modified NCEP definition metabolic syndrome and its individual features on cardiovascular and coronary heart disease both in a cross-sectional analysis and in a prospective, five-year community-based study of people with newly diagnosed type 2 diabetes.

Study Methods

Study Participants

The participants of this study were drawn from members of the original Poole Diabetes Study cohort aged 30 years or above and less than 75 years at diagnosis. Nine (1.6%) were unable to participate. Hence, 562 (332 male, 230 female) individuals entered the cross-sectional analysis and the remaining 428 (241 male, 187 female) participants after exclusion of those with pre-existing cardiovascular disease (n=112) or registration outside the Dorset Health Authority during the course of the study (n=22) were entered into the prospective analysis.

Design

Metabolic syndrome was identified on NCEP criteria (waist circumference (men>102cm; women>88cm), triglycerides (≥1.7mmol/l), HDL cholesterol (men<1.03mmol/l; women<1.29mmol/l), blood pressure (≥135/≥85mmHg), and fasting glucose (≥6.1mmol/l)) except for waist circumference where a body mass index (BMI) equivalent was substituted. The cut-off value for men was set at >28.8 Kg/m^2 based on values used in the West of Scotland Prevention Study (WOSCOPS) [78] and >26.7 Kg/m^2 for women from the cut-off adopted in the Women's Health Initiative Study [80] which were shown to be equivalent to the NCEP waist circumference criteria. People on antihypertensive drug therapy were included in the category with raised blood pressure, as was recommended in the NCEP definition [24]. The presence of more than two of the five criteria defined the presence of the metabolic syndrome.

Pre-existing cardiovascular disease was defined as evidence of a cardiovascular illness during the note review process and/or interview, or the

presence of probable myocardial infarction on the ECG based on the Minnesota code. The study closed on 31st July 2001 with a mean follow-up of 4.2 (SD ±0.6) years. Coronary (ICD9 codes 410-414) and cardiovascular (ICD9 codes 390-459) mortality and morbidity during the study was determined in study participants.

Incident cardiovascular and incident coronary events were recorded and analysed independently, and subsequent events were excluded from the data analysis. Pre-defined end-points were used to identify cardiovascular events both at baseline and during the course of the study (**Table 2.1**). Treatment changes from diagnosis were collected and analysed.

A cross-sectional analysis was performed at the time of diagnosis to investigate the prevalence of the metabolic syndrome and its individual features. The prevalence of CVD and CHD in those with and without the metabolic syndrome was calculated and the odds ratio (OR) for the presence of the metabolic syndrome for each of these outcomes determined after adjustment for age, gender, smoking status and total cholesterol. Unadjusted odds ratios in those aged above 50 years were also determined to allow direct comparison with the results from the NHANES III dataset [79].

In the prospective analysis, the hazard ratio (HR) for the presence of the metabolic syndrome after adjustment for age, gender, smoking status, total cholesterol, anti-platelet therapy, anti-hypertensive therapy, and lipid-lowering therapy was determined both for incident CVD and for CHD. A further analysis based on the number of features of the metabolic syndrome and incident CVD and CHD outcomes was performed. Therapy related data were treated as categorical variables and adjusted for in those individuals who remained event-

free during the study, or when the therapeutic intervention was instituted prior to the CVD or CHD event but not consequent to it.

The East Dorset Local Research Ethics Committee approved the study protocol and informed consent was obtained from all the participants.

Statistical Methods

All data was analysed using SPSS version 12.0. Summary statistics are presented as means (SE) for continuous measures or median (interquartile range (IQR)) for measures with a skewed distribution and frequency (percentage) for discrete measures. Cross-sectional odds ratios were analysed using binary logistic regression and in the prospective analysis, a Cox regression model was employed. Fisher's exact test was used to compare discrete measures and proportions.

Results

The baseline characteristics of participants in the cross-sectional and prospective analyses are summarised in **Table 5.1**. The prevalence of the NCEP-defined metabolic syndrome in people with newly diagnosed diabetes was very high in both studies (82.9% in the cross-sectional analysis and 82.5% in the prospective). There was a greater prevalence of the metabolic syndrome in women than in men at the time of diagnosis of type 2 diabetes (89.9% vs. 78.2% ($p<0.001$) in the cross-sectional study and 90.3% vs. 76.3% ($p<0.001$) in the prospective study). Participants with the metabolic syndrome were comparatively younger than those without metabolic syndrome, (at the time of diagnosis of type 2 diabetes) both in the cross-sectional and in the prospective analyses [(58.9 vs. 62.8 ($p=0.001$) and 57.8 vs. 62.5 ($p=0.01$) respectively)].

Results of the cross-sectional study

The overall prevalence of CVD at diagnosis of type 2 diabetes was 20.1% and of CHD was 14.2 %. After adjusting for age, gender, total cholesterol and smoking status, the presence of the metabolic syndrome was an independent predictor of CVD (OR 2.54 (95% CI 1.31 - 4.93; $p=0.006$)) and CHD (OR 4.06 (95%CI 1.66 - 9.92; $p=0.002$)). In those aged above 50 years and prior to adjustment for age, gender, total cholesterol and smoking status, the presence of the metabolic syndrome was still strongly associated with both CVD (OR 2.07 (95%CI 1.04-4.2; $p=0.026$)) and CHD (OR 3.02 (95% CI 1.21-8.04; $p=0.01$)).

Results of the prospective study

Forty (9.3%) participants died during the course of the study (cardiovascular disease was the underlying cause in eighteen (45%)). Ninety-eight incident cardiovascular events occurred during the course of the study (angina - 37,

fatal/non-fatal MI - 11, cerebrovascular disease- 21 (strokes - 9, TIAs - 12), peripheral vascular disease - 17, and heart failure - 12). Sixty incident CHD events occurred (angina - 47 and myocardial infarction = 13). Participants suffering a non-CHD (as defined in the study protocol) cardiovascular event followed by an incident CHD event explain the difference in the number of angina and MI events in CVD and CHD as these two study end-points were analysed independently.

In relation to therapeutic interventions in study participants initiated prior to an incident CVD event or who remained event-free, lipid lowering therapy was two and a half times more common in individuals with the metabolic syndrome as compared to those without (29% vs. 11.5%; p=0.004), anti-hypertensive use one and a half times as common (51.7% vs. 32.8%; p=0.01) and anti-platelet therapy did not differ between the two groups (11.5% vs. 14.8%; p=0.515).

Unadjusted incident CVD rates were 69.3/1000 patient year follow-up in those with the metabolic syndrome and 54.6/1000 in those without the metabolic syndrome. For men, the crude figures were 81.6/1000 and 63.2/1000, respectively (HR 1.29; p=0.43), and for women, 56.1/1000 and 30.1/1000, respectively (HR 1.87; p=0.39).

Prior to adjustment for other factors in the Cox regression model, the presence of the metabolic syndrome did not predict incident CVD events (HR 1.27 (95%CI 0.72 - 2.23; p=0.41)) or incident CHD events (HR 1.14 (95%CI 0.56 - 2.31; p=0.72)). However, after adjustment for age, gender, smoking status, total cholesterol, anti-platelet therapy, anti-hypertensive therapy, and lipid-lowering therapy, the metabolic syndrome was an independent predictor of

incident CVD (HR 2.05 (95%CI 1.13 - 3.74; p=0.019)). Increasing age (HR 1.07, p<0.001), female gender (HR 0.62, p=0.032), total cholesterol (HR 1.43, p=0.01), and lipid-lowering therapy (HR 0.32, p<0.001) were the other significant independent predictors of risk. After adjustment for the same factors, the hazard ratio for CHD (HR 1.94 (95%CI 0.92 - 4.09; p=0.07)) showed the same trend but failed to reach conventional statistical significance. An increase in the number of features of the metabolic syndrome was associated with a linear increase in the risk of an incident CVD event (p for trend = 0.044). There was nearly a fivefold increase in the level of risk for those possessing all five features of the metabolic syndrome when compared to individuals with just diabetes (HR 4.76 (95% CI 1.10 -21.03; p = 0.042)).

Table 5.2 details the results of the cross-sectional and prospective studies and **Fig. 5.1** shows the adjusted survival curve over time for incremental increases in numbers of features of metabolic syndrome identified at baseline.

Table 5.1 Characteristics of the participants in the cross-sectional and prospective studies both with and without the metabolic syndrome.

	Cross-sectional Analysis		Prospective Analysis	
	Metabolic Syndrome n=462 (82.9%)	No Metabolic Syndrome n=95 (17.1%)	Metabolic Syndrome n=353 (82.5%)	No Metabolic Syndrome n=75 (17.5%)
Age (years)	58.9 (0.5)	62.8 (1.0)	57.8 (0.6)	62.5 (1.2)
Males (%)	258 (55.8)	72 (75.8)	184 (52.1)	57 (76.0)
Females (%)	204 (44.2)	23 (24.2)	169 (47.8)	18 (24.0)
Systolic BP (mmHg)	142.5 (1.0)	134.0 (2.0)	143.0 (1.1)	134.7 (2.5)
Diastolic BP (mmHg)	81.5 (0.6)	77.4 (1.2)	82.2 (0.6)	77.6 (1.5)
Total cholesterol (mmol/l)	5.9 (0.1)	5.5 (0.1)	5.9 (0.1)	5.5 (0.1)
Triglycerides (mmol/l)	2.3 (1.3)†	1.3 (0.5)†	2.2 (1.3)†	1.3 (0.5)†
HDL cholesterol (mmol/l)	1.11 (0.02)	1.31 (0.03)	1.13 (0.01)	1.34 (0.04)
LDL cholesterol (mmol/l)*	3.7 (0.1)	3.4 (0.1)	3.7 (0.1)	3.4 (0.1)
TC: HDL ratio	5.7 (0.1)	4.3 (0.1)	5.7 (0.1)	4.2 (0.1)
HbA_{1C} % at diagnosis	10.6 (0.1)	10.3 (0.3)	10.6 (0.1)	10.1 (0.3)
BMI at diagnosis (kg/m^2)	32.2 (0.3)	26.3 (0.4)	32.6 (0.4)	25.9 (0.4)
Active Smokers (%)	78 (16.9)	23 (24.2)	77 (21.8)	23 (24.2)
Anti-hypertensives(%)	211 (45.7)	27 (28.4)	122 (34.5)	14 (14.7)

Mean (±SE) or n(%) unless otherwise stated.
†Median (Interquartile Range)
* Not calculated in those individuals with a triglyceride level greater than 4.5mmol/l.

Table 5.2 Results of the cross-sectional and prospective studies.

	Metabolic Syndrome (MetS)	No Metabolic Syndrome (No MetS)
Cross-sectional Study		
Prevalence of CVD	99/465 (21.3%)	13/97 (13.4%)
Prevalence of CHD	70/369 (19.0%)	6/83 (7.2%)
OR for CVD	1.75 (95% CI 0.94 - 3.27; p=0.080)	
OR for CHD	2.82 (95% CI 1.19 - 6.70; p=0.018)	
OR for CVD*	2.54 (95% CI 1.31 - 4.93; p=0.006)	
OR for CHD*	4.06 (95%CI 1.66 - 9.92; p=0.002)	
Prospective Study		
CVD events /1000 pt. years	69.3	54.6
CHD events /1000 pt. years	38.9	34.2
HR for CVD	1.27 (95%CI 0.72 - 2.23; p=0.410)	
HR for CHD	1.14 (95%CI 0.56 - 2.31; p=0.720).	
HR for CVD*	2.00 (95%CI 1.10 - 3.62; p=0.022)	
HR for CHD*	1.86 (95%CI 0.88 - 3.91; p=0.103)	
HR for CVD†	2.05 (95%CI 1.13 - 3.74; p=0.019)	
HR for CHD†	1.94 (95%CI 0.92 - 4.09; p=0.070)	

OR - Odds ratio (MetS v. No MetS)
HR - Hazard ratio (MetS v. No MetS)
*after adjustment for age, gender, total cholesterol, smoking status.
†after adjustment for age, gender, total cholesterol, smoking status, lipid-lowering, anti-platelet and anti-hypertensive therapy

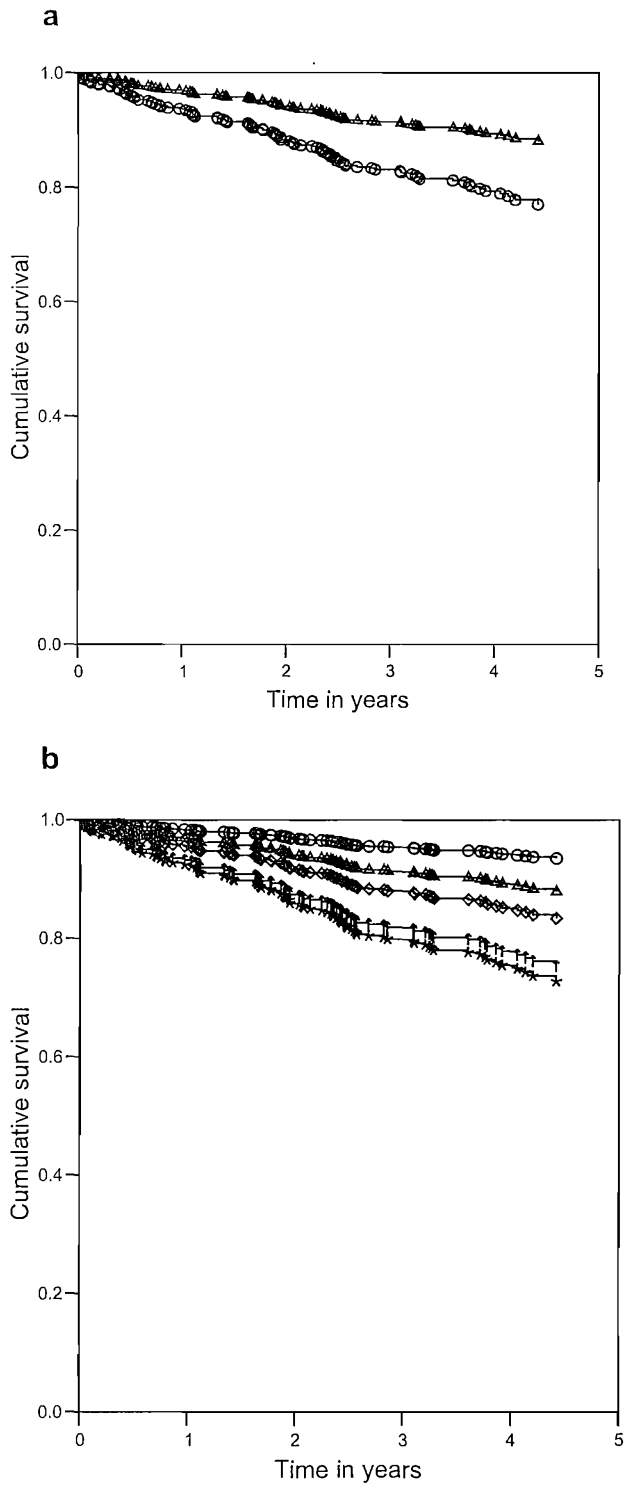


Fig. 5.1 Effect of metabolic syndrome on CVD -free survival in patients with newly diagnosed type 2 diabetes **a.** Survival curves after adjustment for age, gender, smoking status, total cholesterol, anti-platelet therapy, antihypertensive therapy, and lipid-lowering therapy (metabolic syndrome, *circles*; no metabolic syndrome, *triangles*). Hazard Ratio (HR) 2.05; p=0.019. **b.** Survival curves for number of metabolic syndrome features present after adjustment for other factors (one feature, *circles*; two, *triangles*; three, *diamonds*; four, *arrows*; five, *stars*). P for trend = 0.044. Since all study participants have type 2 diabetes, the minimum number of features present is one. Incremental hazard ratios (p value) for two, three, four and five features of the metabolic syndrome vs. one feature (diabetes) alone – 1.93 (0.39), 2.71 (0.18), 4.23 (0.56), 4.76 (0.042).

Discussion

The novel results of our study demonstrate that using modified NCEP criteria, metabolic syndrome is associated with an increased risk of CVD events in the first five years following diagnosis of type 2 diabetes. Survival was incrementally and progressively worse with increasing numbers of features of the syndrome (**Fig 5.1**). This finding clearly demonstrates the continuum of risk seen with increasing features of the metabolic syndrome.

Our cross sectional data confirm the findings of Alexander et al [79] from the NHANES dataset, despite differences in study design with respect to age cut-offs and diagnostic criteria for CHD. The prevalence of the metabolic syndrome in our cohort with newly diagnosed type 2 diabetes was 82.9% as compared to 86% in the diabetic subset from the NHANES III dataset. In the NHANES sub-group, it is likely that diabetes would have been present for markedly varying lengths of time, prior to identification of metabolic syndrome features. In our study, the odds ratios for metabolic syndrome and CHD in the diabetic population aged over 50 were increased by a factor of three, which is similar to the level of risk seen in the diabetic subset in NHANES III. Adjusting for age and gender, the presence of metabolic syndrome conferred a 2.5 fold increase in the risk of CVD at diagnosis of type 2 diabetes, and a 4 fold increase in the risk of CHD. The results of the cross-sectional study demonstrates that people with newly diagnosed type 2 diabetes who additionally possess the metabolic syndrome tend to be younger, and that at diagnosis, a greater proportion of women than men have the metabolic syndrome. The increased prevalence of the metabolic syndrome in women with newly diagnosed type 2 diabetes related mainly to the

greater proportion exceeding the body mass index and HDL cholesterol thresholds of the metabolic syndrome criteria. This could reflect gender differences relating to the impact of obesity on glucose homeostasis, lipid sub-fractions and atherosclerosis [81,82] and requires further study in a larger cohort.

As mentioned by Alexander et al., a cross-sectional analysis is subject to survival bias and causality cannot be inferred [79]. The prospective study was designed to address this issue in relation to people with newly diagnosed diabetes. The results of this study lend further weight to evidence from the UKPDS [32] that hyperglycaemia per se may have only a relatively small contribution to CVD in type 2 diabetes when compared to other features of the metabolic syndrome. Clearly, metabolic syndrome remained a strong predictor of cardiovascular disease after adjustment for age, gender, cigarette smoking, total cholesterol, and therapy. However, there was an attenuation of the hazard ratios when results from the prospective analyses were compared with the cross sectional study. This effect was more marked for risk of CHD than CVD in the prospective study, where metabolic syndrome predicting CHD events failed to achieve conventional levels of statistical significance. The relatively small number of events is one possible explanation for this finding. Alternative explanations for this finding may be a "survivor" effect and a differential absolute benefit of lipid-lowering therapy on risk of CHD in people with and without the metabolic syndrome as seen in a subgroup analysis of the Scandinavian Simvastatin Survival Study [83].

Unlike results from the cross-sectional study, in the prospective follow-up, the unadjusted risk of CHD was not significantly increased. This finding is most

likely attributable to the considerably greater usage of lipid-lowering therapy in the metabolic syndrome group after diagnosis of type 2 diabetes (as occurred in our study) and may be particularly relevant and important data from the public health standpoint as it strengthens the case for achieving recommended treatment goals in this high-risk population.

Importantly, we have also shown a clear incremental increase in cardiovascular disease risk with increasing features of the metabolic syndrome in people with newly diagnosed type 2 diabetes. As each feature of the metabolic syndrome criteria is a proven cardiovascular risk factor [84,85], these results show clearly that increasing numbers of metabolic syndrome features equate to increasing risk. This finding could offer a simple and pragmatic clinical addition to the multi-factorial risk assessment methods as used in the United Kingdom and elsewhere in Europe [21,23,85,86]. We have previously published the sensitivity and specificity of the UKPDS-derived, 15% 10-year CHD risk threshold for incident cardiovascular disease in this study population [87]. Interestingly, the use of a combination of the presence of both metabolic syndrome and a 15% 10-year CHD risk threshold results in a small, statistically non-significant reduction in sensitivity [0.80 (0.72 - 0.86) vs. 0.90 (0.82 - 0.95)] and a significant increase in specificity [0.45 (0.43 - 0.47) vs. 0.30 (0.25 - 0.36)] for new-onset cardiovascular disease.

We have studied all patients with newly diagnosed diabetes in a defined community and the results reflect usual clinical practice in both hospital and primary care. A limitation of the study is usage of a BMI equivalent instead of waist circumference. However, we believe that the presence of glucose

dysregulation would mean that participant body weight is likely to correlate closely with central adiposity and not reflect increased muscle mass. Furthermore, patients with diabetes may find a weight and height measurement less intrusive than waist circumference measurement and waist circumference is more likely to be subject to measurement error than BMI. Conversely, accurate waist circumference measurement may well be a useful measure for patient self-care and is, in itself, an area of physician-patient interaction that needs to be explored.

In conclusion, we have shown that using modified NCEP criteria, metabolic syndrome is associated with an increased risk of incident cardiovascular disease in the first five years following diagnosis of type 2 diabetes. Survival incrementally and progressively worsens with the number of features of the metabolic syndrome that are present. Reversing the features of the metabolic syndrome should be a useful therapeutic target in these individuals.

CHAPTER 6

Socioeconomic deprivation independently predicts incident cardiovascular disease in people with newly diagnosed type 2 diabetes.

Introduction

Following the publication of the original Whitehall Study of civil servants in the late 1970s [25], it was evident that in the general population, the incidence of coronary heart disease varies with socioeconomic status. Since then, several other studies have clarified the relationship between deprivation (using a variety of measures) and increased cardiovascular and cause-specific mortality [88-91].

In the general population, it has been shown that traditional cardiovascular risk factors accounts for around a third of the increased hazard of cardiovascular disease seen in people of lower socioeconomic status [25].

In people with diabetes, the impact of deprivation on all-cause mortality has been reported in some detail. Most of these studies confirm the presence of a socioeconomic gradient [92-95], although an Italian study provided conflicting results [96]. Additionally, a Finnish study initially failed to show a relationship between deprivation and increased mortality [97], but this became apparent on subsequent follow-up [98].

Cross-sectional studies have shown an association between microvascular and macrovascular complications of diabetes and indicators of deprivation [95,99,100]. However, the relationship between incident cardiovascular disease and deprivation in people with type 2 diabetes has not been studied.

We have explored the relationship between geographical indices of deprivation and incident cardiovascular disease in a prospective, five-year community-based study of people with newly diagnosed type 2 diabetes.

We have previously published a report on the association between cardiovascular disease and the metabolic syndrome in people with newly

diagnosed type 2 diabetes [101]. Since obesity is a prime component of the metabolic syndrome and is positively associated with deprivation in people with diabetes [95,102], we have investigated whether modified NCEP (National Cholesterol Education Program) criteria-defined metabolic syndrome at baseline [24], the 10-year Framingham coronary heart disease risk score [20], and cigarette smoking account for the association between deprivation and cardiovascular disease in people with newly diagnosed type 2 diabetes. If this is not the case, traditional methods of appraising cardiovascular risk will fail to appreciate an increased hazard in people with type 2 diabetes who are materially deprived.

Study Methods

Study Subjects

The study participants in this analysis are the same as those described in **Chapter 4.**

Design

Metabolic syndrome (MetS) was identified on modified NCEP criteria as described in **Chapter 5.** Deprivation was assessed from a geographical index of deprivation by matching the residence postcode at study enrolment to an enumeration district (which is a census block comprising of around 150 households) and matching the enumeration district to its Townsend score in the 1991 census dataset [103,104]. The Townsend score is a measure of the level of material deprivation and includes four variables: unemployment (lack of material resources and insecurity), overcrowding (material living conditions), lack of owner occupied accommodation (a proxy indicator of wealth), and lack of car ownership (a proxy indicator of income). The score is a summation of the standardised scores (z scores) for each variable. The cohort was split into two groups - more deprived (MD) and less deprived (LD) comprising scores above and below the median value.

Incident cardiovascular events were recorded and analysed as in **Chapter 4** and subsequent events were excluded from the data analysis. The pre-defined end-points used to identify cardiovascular events are detailed in **Table 2.1.** Therapy data relate to interventions prior to a CVD event or instituted in those individuals who remained event-free during the study. Therapeutic interventions introduced subsequent to a CVD event were not included.

After adjusting for age and gender, hazard ratios (HR) for incident cardiovascular by deprivation group were calculated. Hazard ratios after a further adjustment for MetS (both by considering MetS as a categorical variable and by treating the individual features as continuous variables) and cigarette smoking at diagnosis were calculated. The hazard ratio was then adjusted for the 10-year Framingham CHD risk score [20], as well. Additionally, the proportion of events underestimated by the Framingham risk function in both the deprivation groups was calculated. Changes in metabolic parameters between the time of study entry and the close of the study in those who remained CVD-free throughout were ascertained. Individuals who had complete data available within 6 months of the closing date of the study were included in this part of the analysis (n=306, missing = 24 (7.3%)).

Statistical Methods

All data was analysed using SPSS version 14.0. Summary statistics are presented as means (SE) for continuous measures or median (interquartile range (IQR)) for measures with a skewed distribution and frequency (percentage) for discrete measures. Cox regression was used to describe the association between deprivation and cardiovascular outcomes. Fisher's exact test was used to compare discrete measures and proportions.

Results

Table 6.1 describes the baseline characteristics of the 428 participants (241 males and 187 females, comprising 94% of the original cohort) split into MD and LD groups. Study participants in the MD group had an increased prevalence of MetS, a significantly higher body mass index, systolic blood pressure, and LDL cholesterol levels at the time of diagnosis of type 2 diabetes as compared to those in the LD group.

Forty (9.3%) participants died during the course of the study (cardiovascular disease was the underlying cause in eighteen (45%)). Ninety-eight incident cardiovascular events occurred during the course of the study (angina - 37, fatal/non-fatal MI - 11, cerebrovascular disease- 21 (strokes - 9, TIAs - 12), peripheral vascular disease - 17, and heart failure - 12).

After age and gender adjustment, the hazard ratio (HR) for incident cardiovascular disease in the MD group was 1.76 (95%CI 1.17-2.65; p=0.006) compared to the LD group (**Fig. 6.1**). Splitting the cohort by quartiles of the deprivation scores, there was more than a doubling of the hazard of incident cardiovascular disease between the most and the least deprived quartile (HR 2.19 (95%CI 1.23-2.89; p=0.008).The hazards for the second and third quartile (compared to the least deprived) were 1.27 (95%CI 0.67-2.41) and 1.79 (95%CI 0.99-3.25) with a significant trend (p=0.032).

Adjusting for MetS as a categorical variable and cigarette smoking (**Fig. 6.2a**), there was a marginal reduction in the hazard for MD vs. LD (HR 1.66 (95%CI 1.10-2.50; p=0.016)). A similar limited effect was seen after adjustment of the survival analysis for cigarette smoking and the individual continuous

variables comprising MetS (**Fig. 6.2b**) (HR 1.60 (95%CI 1.07-2.41; p=0.025)). **Fig. 6.3** describes the survival curves after adjusting for all these factors and the 10-year Framingham CHD risk score (HR 1.54 (95%CI 1.02-2.32; p=0.042). Thus, age, gender, MetS covariates, tobacco use, and the 10-year Framingham CHD score account for around 30% of the increased hazard shown in **Fig. 6.1**

The Framingham risk function for cardiovascular disease underestimated observed incident cardiovascular events in the LD group by 15.8%, a figure that did not achieve conventional statistical significance (predicted events (n=32) observed events (n=38); p=0.254). In the MD group, the degree underestimate increased threefold to 43.3% (predicted events (n=34) observed events (n=60); p<0.001).

Aspirin prescribing did not differ between the MD and LD groups (29 (13.6%) vs. 24 (11.2%); p=0.560 respectively). Neither did the prescribing of anti-hypertensives (111 (51.9%) vs. 99 (46.3%); p= 0.288) or that of lipid-lowering agents (50 (23.4%) vs. 49 (22.9%); p=1.000).

At the end of the study and in those who remained free of clinically evident CVD, participants in the MD group had a higher mean systolic blood pressure than those in the LD group (148.8 vs. 142.5 mmHg; p=0.006), higher BMI (32.9 vs. 30.8 Kg/m^2; p=0.005) and elevated 10-year Framingham CHD risk scores (20.1 vs. 16.5 %; p=0.002). Aspirin prescribing (14.2% vs. 10.2%; p=0.311), anti-hypertensive prescribing (51.3% vs. 45.4%; p=0.321) and prescribing of lipid-lowering agents (26.7% vs. 24.7%; p=0.706) did not differ between CVD-free survivors in the two groups. MetS prevalence was 85.1% in the MD group and 75.3% in the LD group (p=0.042).

Table 6.2 details the change in metabolic parameters at the end of the study in those who remained free of clinically evident CVD. Participants in the MD group had a significant increase in BMI (+0.88Kg/m^2 (SE±0.27); p=0.001) and serum triglycerides (+0.37mmol/l (SE±0.18); p=0.038).

Table 6.1 Baseline characteristics of the participants in the MD and LD groups of the study.

	More Deprived (MD) n=214	Less Deprived (LD) n=214	p
Age (years)	58.2 (0.8)	59.0 (0.7)	0.440
Males (%)	117 (54.7)	124 (57.9)	0.559
Females (%)	97 (45.3)	90(42.1)	0.276
Systolic Blood Pressure (mmHg)	143.5 (1.4)	139.5 (1.4)	0.045
Diastolic Blood Pressure (mmHg)	81.9 (1.0)	80.9 (0.9)	0.396
TC: HDL ratio	5.54 (0.12)	5.26 (0.11)	0.079
LDL cholesterol (mmol/l)*	3.74 (0.07)	3.54 (0.06)	0.037
Triglycerides (mmol/l)	2.05(1.3)†	2.52 (1.4)†	0.863
HbA_{1C} % at diagnosis	10.6 (0.2)	10.5 (0.2)	0.555
BMI at diagnosis (kg/m2)	32.3 (0.5)	30.6 (0.4)	0.013
Active Smokers (%)	53 (24.8)	47 (22.0)	0.568
MetS at diagnosis (%)	185 (86.4)	168 (78.5)	0.041
Framingham 10-year CHD risk	22.6 (0.8)	21.5 (0.8)	0.329

Mean (±SE) or n(%) unless otherwise stated.
†Median (Interquartile Range)
* Not calculated in those individuals with a triglyceride level greater than 4.5mmol/l (n=388 as 40 participants had TG> 4.5mmol).

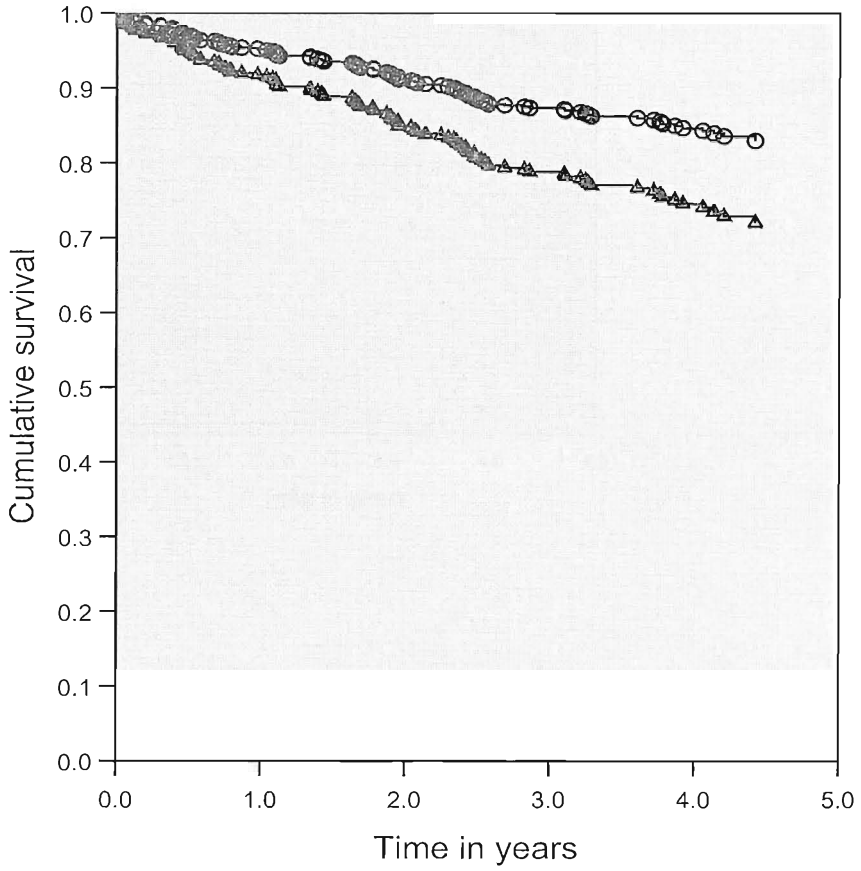
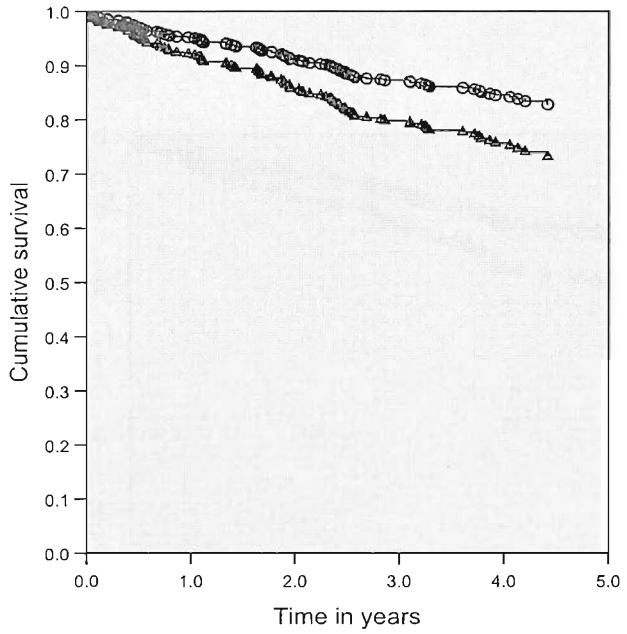


Fig 6.1 Effect of deprivation on CVD -free survival in patients with newly diagnosed type 2 diabetes after adjustment for age and gender (less deprived (LD), *circles*; more deprived (MD), *triangles*). Hazard ratio (HR) for incident cardiovascular disease in the MD group was 1.76 (95%CI 1.17-2.65; p=0.006) compared to the LD group.

a



b

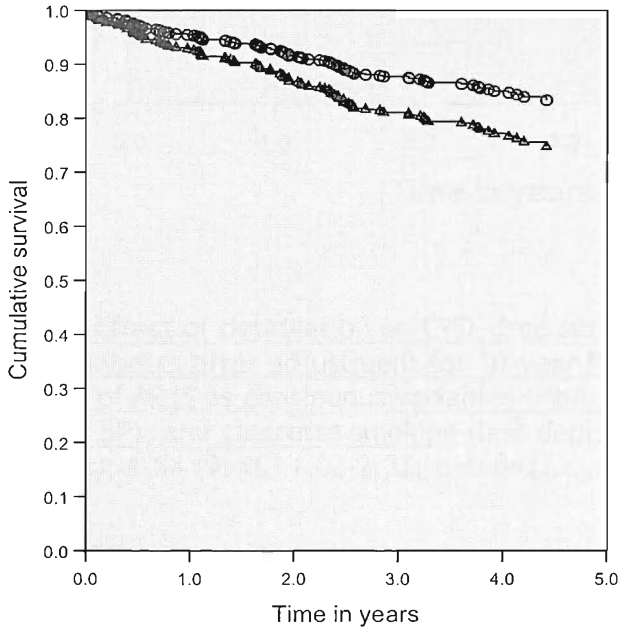


Fig. 6.2 Effect of deprivation on CVD -free survival in patients with newly diagnosed type 2 diabetes after adjustment for age, gender, MetS, and cigarette smoking (less deprived (LD), *circles*; more deprived (MD), *triangles*). **a.** Survival curves after adjustment for MetS as a categorical variable; HR = 1.66 (95%CI 1.10-2.50; p=0.016). b. Survival curves after adjustment for individual features of MetS as continuous variables (HbA_{1C} , BMI, triglycerides, HDL, systolic BP and diastolic BP); HR =1.60 (95%CI 1.07-2.41; p=0.025).

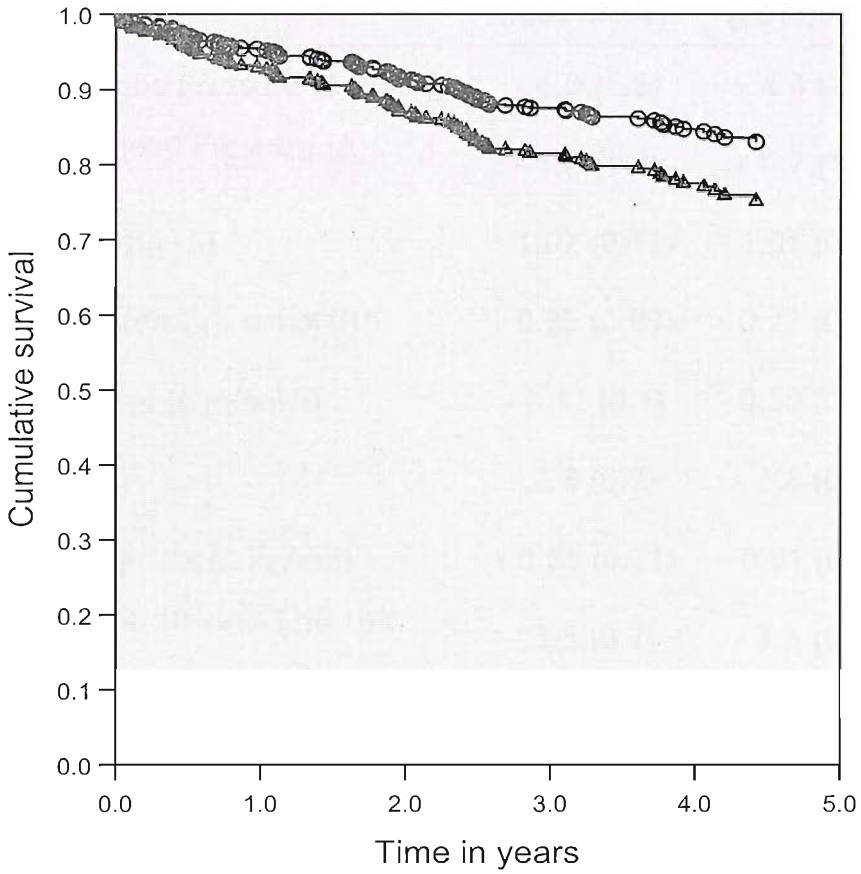


Fig. 6.3 Effect of deprivation on CVD -free survival in patients with newly diagnosed type 2 diabetes after adjustment for 10-year Framinghm CHD risk score, individual features of MetS as continuous variables (HbA_{1C} , BMI, triglycerides, HDL, systolic BP and diastolic BP), and cigarette smoking (less deprived (LD), *circles*; more deprived (MD), *triangles*); 1.54 (95%CI 1.02-2.32; p=0.042).

Table 6.2 Changes in baseline metabolic parameters from study entry to study close in those individuals who remained free of clinically evident CVD.

	More Deprived (MD) n=147	Less Deprived (LD) n=159	p
Systolic Blood Pressure (Δ mmHg)	+ 6.0 (1.8)	+ 4.4 (1.6)	0.509
Diastolic Blood Pressure (Δ mmHg)	+ 1.3 (1.3)	+ 0.7 (1.0)	0.691
TC: HDL ratio (Δ)	- 1.02 (0.12)	- 1.01 (0.12)	0.948
LDL cholesterol (Δ mmol/l)*	- 0.25 (0.09)	- 0.22 (0.08)	0.851
Triglycerides (Δ mmol/l)	- 0.12 (0.1)	- 0.50 (0.15)	0.038
HbA_{1C} (Δ %)	- 2.8 (0.2)	- 2.8 (0.2)	0.995
BMI at diagnosis (Δ kg/m2)	+ 0.88 (0.21)	+ 0.01 (0.18)	0.001
Framingham 10-year CHD risk (Δ%)	- 3.5 (0.7)	- 3.6 (0.5)	0.889

Mean (±SE) or n(%) unless otherwise stated.
* Not calculated in those individuals with a triglyceride level greater than 4.5mmol/l.

Discussion

Our novel results clearly show that a geographical index of material deprivation is independently associated with an increased risk of incident cardiovascular disease in people with newly diagnosed diabetes. There is a doubling of hazard between the least and most deprived quartiles. Of particular note, metabolic syndrome at diagnosis of type 2 diabetes and cigarette smoking have little impact on the cardiovascular hazard associated with increasing deprivation. In fact, tobacco use, individual features of the metabolic syndrome at baseline, and the 10-year Framingham CHD risk score (used to integrate other traditional risk factors) account for less than a third of the increase in hazard.

We have previously published the performance of the Framingham risk score in this cohort demonstrating that the score underestimates overall cardiovascular risk by approximately a third [87]. Our findings in the present study are complementary and reveal a threefold increase in the degree of underestimation by the scoring system in the more deprived half of the study cohort as compared to the less deprived group. Since risk scores are primarily used to prioritise treatment, the neglect of deprivation may greatly compromise the effectiveness of risk-scoring methods and exacerbate health inequalities among the more materially deprived members of society.

Prescribing rates of therapeutic interventions did not differ between more and less materially deprived study participants. However, a gradient in cardiovascular risk factors was seen between the more and less deprived groups at baseline and it is conceivable that the similar prescribing rates may actually conceal a relative inadequacy of treatment in the more deprived population.

Given the relatively small number of individuals studied, we are unable to comment on this issue with any degree of certainty. Studies looking at health care access [105], health service usage [106,107], cardiovascular risk factors [102,108-110], differences in care providers [111] and their association with level of deprivation in the general population would suggest that this remains a possibility.

Several explanations for the gradient in health outcomes and deprivation have been proposed. These explanations range from lifestyle behaviours such as smoking [109,112,113], unhealthy dietary habits [114], obesity [115], and sedentary lifestyles [110,112,115]. Factors affecting effective use of healthcare services such as access to high-quality health care [111] because of the "inverse care law" [116], and the ability of individual patients to comprehend and comply with complex preventative therapeutic strategies [111] while coping with the wider social consequences of diminished financial means have also been proposed, as well. Psychosocial factors relating to workplace stress, job insecurity, social exclusion and even sleep quality have been suggested as alternative explanations [117-122]. The mechanism underlying the link between deprivation and poor health is likely to be multifactorial. Given the complex self-management demands and healthcare needs of people with diabetes, it is relatively unsurprising that deprivation adversely affects both vascular and mortality outcomes in this group of patients.

We performed an exploratory analysis of the changes in metabolic parameters in CVD-free survivors from the start to the finish of the study. Those participants with incident CVD events were excluded, as they are likely to have been prescribed a range of therapeutic interventions following recognition of

clinical CVD and this would greatly affect overall metabolic outcomes noted at the end of the study. At the close of the study, more deprived individuals continue to have higher 10-year CHD-risk scores. Furthermore, we have shown that more deprived patients increased their body weight by a significantly greater amount over the course of the study than did those who were less deprived. Although this analysis is likely to be affected by a "survivor" bias, the bias should tend to minimise differences in cardiovascular risk factors between the two deprivation groups and our results may hence underestimate the impact of deprivation on metabolic outcomes. Weight gain, possibly because of nutritional factors, may underlie the accumulation of obesity-related cardiovascular risk factors in deprived individuals following diagnosis of type 2 diabetes. Putatively, this might explain some of the persistent increased cardiovascular risk seen in more deprived participants. If this is the case, nutritional advice and interventions relating to increasing physical activity may be of particular importance to patients who are more deprived and available resources may well need to be targeted at this patient sub-group.

We have studied all patients with newly diagnosed diabetes in a defined community and the results reflect usual clinical practice in both hospital and primary care. Ethnicity is not a factor in this study, as among the cohort members, only two individuals failed to describe themselves as white. A limitation of the study is usage of a BMI equivalent instead of waist circumference as part of the definition of MetS. However, we believe that the presence of glucose dysregulation would mean that participant body weight is

likely to correlate closely with central adiposity and not reflect increased muscle mass.

Our results do suggest that, a measure of deprivation should be included when assessing cardiovascular risk in people with newly diagnosed type 2 diabetes. However, the lack of a consistent definition of deprivation and the wide variety of proxy measures of socioeconomic deprivation including social class [97,98], job status [25,95], educational status [100,102], and geographical indices relating to small area statistics [105,111,112] that have been used in the medical literature point to the difficulties in effectively assessing this characteristic. Furthermore, deprivation, be it psychosocial or material, is dependent on the cultural context as well as being defined by the prevalent culture. In our study, we have used a geographical index of deprivation in the form of the Townsend score [103]. This has been validated as an effective measure of material deprivation in a number of cohort studies. However, geographical indices or small area statistics are prone to the "ecological fallacy" (individual families within the same residential postcode may not always share socioeconomic status) and the score may well fail to discern the degree of deprivation at the individual level. In the context of the study, splitting the scores into two groups will have reduced the chances of misallocation of individuals to an inappropriate level of material deprivation. This approach may well be inaccurate when applied to the assessment of an individual's level of cardiovascular disease risk. Individual deprivation scores may be more appropriate in the clinical setting and this is an area for further study. One such scoring system, the EPICES score, was

shown to be associated with poor glycaemic control and microvascular complications in a small cross-sectional study in people with diabetes [99].

Nonetheless, we believe that ignoring the effect of deprivation in type 2 diabetes will exacerbate healthcare inequalities and worsen the socioeconomic gradient of health. Effective inclusion of a deprivation measure as part of diabetes healthcare delivery should identify health-disadvantaged members of a socially mixed population who may benefit from therapeutic interventions to redress the imbalance.

CHAPTER 7

Mortality in people with newly diagnosed type 2 diabetes compared with local age and sex matched controls

Introduction

Several studies have shown that diabetes is associated with a substantial increase in all-cause mortality [94,123-125]. A large portion of this excess mortality is attributable to cardiovascular causes [126-129]. In addition, effects on cancer mortality and respiratory disease mortality have been described although the findings are inconsistent [124,126,130-132]. Reports from different countries suggest that the impact of diabetes on mortality may vary in relation to the setting and population studied [133]. It is unclear whether the differences between studies relate to the sampling methods or to true geographic variation. There is a need for data on diabetes mortality from a variety of countries, using consistent data collection methods, to allow assessment of patterns of mortality.

It is evident that data should come from unselected populations. Restriction of data collection to either the primary care setting or hospital care is likely to introduce a selection bias. Furthermore, some studies have focussed on subsets of populations with diabetes such as insulin-treated individuals [134]. Additionally, it is well documented that diabetes is grossly underreported on death certificates, which would negatively affect reports based solely on routine national mortality data. Consequently, cohort studies are accepted to be the most suitable means of ascertaining the impact of diabetes on mortality [135]. A further issue relates to the selection of comparator data. Standardised Mortality Ratios (SMR) based on national or regional mortality statistics may not be accurate when the study population is derived from a smaller geographical area, as clarified in a previous study performed in the Poole area [9]. A locally derived

age and gender-matched case-control cohort study design is an effective way of overcoming these limitations.

Duration of diabetes is a potential source of confounding in studies of people with diabetes. Studies restricted to people with a new diagnosis of diabetes will limit the impact of duration, although it is important to appreciate that the onset of diabetes may predate diagnosis by a variable and often substantial period [136]. We are unaware of any studies that have described mortality in people with newly diagnosed type 2 diabetes. Furthermore, data pertaining to patterns and predictors of mortality at this early stage in the disease process may help inform the development of health services for people with diabetes

In this context, we have studied early mortality in individuals with newly diagnosed type 2 diabetes compared to local age and sex-matched controls. We have also studied the predictors of early mortality based on available data at baseline.

Study Methods

Study Subjects

All 736 cohort members and their age/sex matched controls as described in **Chapter 2** were entered into this analysis.

Death registration

The 736 cases and controls were registered with the Office of National Statistics (ONS). Date of death, causes of death, and underlying causes of death were derived from death certificate data. Due to death coding inconsistencies in people with diabetes, the death certificates that had diabetes as the underlying cause of death were recoded using International Classification of Diseases (ICD)-10 rules. This was done after removal of diabetes from the coding except in circumstances where the cause of death was diabetes-specific, like hypoglycaemia. This approach is necessary as the underlying cause of death depends on the physician's choice of ordering the entries on the death certificate.

Design

Data collection ended on September 30th, 2003 and mortality status determined for each individual at a time point of 5.25 years from study entry. This was the minimum follow-up period in the study for all survivors. Mortality data alone was available for the control population.

In view of the effects of therapy on baseline variables, blood pressure and lipids were treated as categorical variables. Elevated blood pressure was defined as anti-hypertensive therapy at diagnosis, and/or a systolic blood pressure ≥140mmHg, and/or a diastolic blood pressure ≥80mmHg. Elevated triglyceride

was defined as lipid-lowering therapy and/or triglycerides ≥1.7 mmol/l. Elevated cholesterol was defined as a total cholesterol ≥5 mmol/l and/or lipid-lowering therapy at diagnosis. Neuropathy was defined as the presence of a VPT >25v at the great toe [137] and proteinuria as ≥ 1+ urine protein on dipstick testing. Townsend scores were split into quartiles for data analysis. Cigarette smoking was defined as present in those who had smoked regularly during the previous twelve months. HbA_{1c}, creatinine, and BMI were treated as continuous variables.

Statistical Methods

Age and gender specific all-cause mortality odds ratios were calculated, using conditional logistic regression, for the cohort with diabetes compared to the matched non-diabetic cohort. Due to the limited numbers, cause-specific mortality odds ratios are reported by gender and not by age banding. Age and sex standardised mortality ratios (SMRs) were calculated for both cases and controls using the Office of National Statistics (ONS) 2001 mortality data for England and Wales as a comparator [138]. The 95% confidence intervals for SMRs were constructed under the Poisson assumption.

Age-adjusted odds ratios were ascertained for each covariate and multivariate analysis was performed using binary logistic regression to identify independent predictors of mortality.

Results

The baseline characteristics of people with newly diagnosed type 2 diabetes are described in **Table 7.1**. Some gender differences in baseline variables were also noted. Women were older at the time of diagnosis (65.9 vs. 62.9 years; $p<0.001$), had a lower BMI (29.6 vs. 31.0 kg/m^2; $p<0.001$), a lower creatinine (80.1 vs. 94.5 μmol/l; $p<0.001$) and a trend towards a higher HbA_{1c} at diagnosis (10.7 vs. 10.3%; $p=0.053$). Furthermore, in relation to categorical variables, fewer women were smokers (11.4 vs. 18.1%; $p=0.013$), and a greater proportion of women had a cholesterol ≥5mmol/l (83.9 vs. 72.7%; $p<0.001$). Other categorical variables (proteinuria, VPT>25v, elevated blood pressure, and elevated triglycerides) were not significantly different in men and women with newly diagnosed type 2 diabetes.

There were 147 deaths in the cohort with diabetes during the study. Of these, the underlying cause of death was coded as cardiovascular in 62 (42.2%), cancer in 31(21.1%) and other causes in 54 (36.7%) individuals. Respiratory disease was prominent in the group consisting of other causes. The crude mortality rate in people with newly diagnosed type 2 diabetes was 41.9/1000 patient-year follow-up.

Diabetes was grossly underreported on the death certificates. Only 41 (28%) of death certificates in the group with type 2 diabetes were coded for diabetes in any of the columns on the standard death certificate. No deaths from hypoglycaemia were reported. This underreporting extended to cardiovascular disease, as well. Based on case note reviews and primary care records, 69% of those with diabetes who died were known to have clinically evident

cardiovascular disease prior to death. Of these and in those where cardiovascular disease was not the underlying cause of death, only 40% were coded for cardiovascular disease in any of the other columns on the standard death certificate.

Odds ratios with 95% confidence intervals in the case-control study are reported in **Table 7.2.** Newly diagnosed type 2 diabetes is associated with an increased risk of death across all studied age bands, including the relatively elderly (aged 75 years and above), although this effect is most pronounced in the lower age-bands with a threefold increase in mortality odds for those aged less than 60 years at diagnosis. Women are particularly affected by a diagnosis of type 2 diabetes, and in this cohort, a sevenfold increase in mortality odds is seen in those aged 60-74 years, and a fourfold increase in those aged less than 60 years (allowing for the wide confidence intervals).

Cause-specific mortality shows a clear increase in risk for those individuals newly diagnosed with type 2 diabetes and this applies to death from cardiovascular disease, cancer deaths, and other mortality. No statistically significant gender differences in cause-specific mortality were seen.

Table 7.3 describes the age and sex standardised mortality ratios (SMRs) for newly diagnosed type 2 diabetes using England and Wales mortality data as a comparator. The cohort with diabetes has only a modest increase in SMR (1.37 (95%CI 1.10 - 1.72)) with this approach. This is explained by the SMRs for the controls that were significantly lower than expected from national mortality statistics (0.76 (95%CI 0.58 - 0.99)).

After age-adjustment, the factors associated with a greater risk of death in a univariate analysis were proteinuria at diagnosis, neuropathy, cigarette smoking, elevated blood pressure, and Townsend deprivation quartiles (**Table 7.4**). All of these variables, along with age, remained in the fitted multivariate model (**Table 7.5**). Townsend quartiles were associated with a 1.4-fold increase in mortality odds for each step. After adjustment for other factors, people with newly diagnosed type 2 diabetes in the most deprived quartile had mortality odds two and a half times greater than the least deprived quartile. All other covariates in the model, barring age, were associated with an approximate doubling of the mortality odds ratio.

Table 7.1 Baseline characteristics of the 736 participants with type 2 diabetes in the study

	Missing (n)	Mean (±SD) or n(%)
Age (years)	0	64.3 (±13.3)
HbA_{1C} (%) at diagnosis	4	10.4 (±2.8)
Gender - Males	0	403 (54.8%)
Creatinine (μmol/l)	5	87.9 (±20.4)
BMI at diagnosis (kg/m^2)	6	30.2 (±6.6)
Elevated Blood Pressure	17	524 (72.9%)
Elevated Cholesterol	20	556 (77.7%)
Elevated Triglyceride	20	462 (64.5%)
Smokers	0	111 (15.1%)
Vibration Perception Threshold>25v	25	99 (13.9%)
Proteinuria	2	70 (9.5%)

Table 7.2 Odds ratios for all-cause and cause-specific mortality in people with newly diagnosed type 2 diabetes compared to controls over a period of 5.25 years

	n	Diabetic Cohort - Mortality (n)	Non-Diabetic Comparison Cohort Mortality (n)	Odds Ratio (OR)	95% CI	*P*
All Cause Mortality						
All	736	147	81	2.47	1.74, 3.49	<0.001
Age <60 years	258	16	5	3.20	1.17, 8.73	0.016
Age 60-74 years	313	52	21	3.00	1.67, 5.38	<0.001
Age ≥ 75 years	165	79	55	2.00	1.24, 3.23	0.004
Males	403	70	42	2.04	1.29, 3.23	0.002
Age <60 years	158	12	4	3.00	0.97, 9.30	0.046
Age 60-74 years	179	29	16	2.00	1.00, 4.00	0.046
Age ≥ 75 years	66	29	22	1.73	0.82, 3.63	0.144
Females	333	77	39	3.11	1.83, 5.29	<0.001
Age <60 years	100	4	1	4.00	0.45, 35.79	0.180
Age 60-74 years	134	23	5	7.00	2.09, 23.47	<0.001
Age ≥ 75 years	99	50	33	2.21	1.18, 4.16	0.011
Cardiovascular Mortality						
All	736	62	34	2.12	1.32, 3.41	0.002
Males	403	31	18	1.93	1.01, 3.68	0.042
Females	333	31	16	2.36	1.17, 4.78	0.014
Cancer Mortality						
All	736	31	14	2.54	1.27, 5.11	0.006
Males	403	14	5	3.25	1.06, 9.97	0.029
Females	333	17	9	2.14	0.87, 5.26	0.088
Other Mortality						
All	736	54	33	1.81	1.12, 2.92	0.014
Males	403	25	19	1.38	0.72, 2.62	0.330
Females	333	29	14	2.50	1.20, 5.21	0.012

Table 7.3 Age and Sex Standardized Mortality Ratios (SMR) based on England and Wales National Mortality Data 2001

	n	SMR (95%CI)
Cases- All	736	1.37 (1.10, 1.72)
Cases - Male	403	1.21 (0.88, 1.66)
Cases - Female	333	1.57 (1.14, 2.18)
Controls	736	0.76 (0.58, 0.99)
Controls - Male	403	0.72 (0.50, 1.05)
Controls - Female	333	0.80 (0.54, 1.18)

Table 7.4 Age-adjusted covariates with odds ratios for all-cause mortality in people with newly diagnosed type 2 diabetes

Covariate	missing (n)	Odds Ratio (95% CI)	*P*
Age alone	0	1.11 (1.08, 1.13)	<0.001
Male Gender	0	0.99 (0.66 -1.49)	0.962
HbA_{1c} at diagnosis (%)	4	0.95 (0.88, 1.01)	0.110
Cigarette Smoking	0	2.18 (1.17, 3.83)	0.013
Elevated Blood Pressure	17	1.94 (1.15, 3.28)	0.014
Elevated Triglyceride ≥ 1.7mmol/l	20	1.03 (0.68, 1.58)	0.879
Cholesterol ≥ 5 mmol/l	20	1.11 (0.68, 1.83)	0.675
BMI	6	0.98 (0.94, 1.02)	0.328
Creatinine	5	1.01 (0.99, 1.02)	0.460
Vibration Perception Threshold >25v	25	1.92 (1.16, 3.17)	0.011
Proteinuria	2	1.90 (1.06, 3.43)	0.032
Townsend Quartiles			0.005[a]
First	0	1.00	
Second	0	1.51 (0.86, 2.66)	0.149[b]
Third	0	1.94 (1.12, 3.34)	0.018[b]
Fourth	0	2.55 (1.30, 5.01)	0.007[b]

[A] Jonckheere-Terpestra test for trend
[b] Odds Ratio vs. First Quartile; First =least deprived and Fourth = most deprived.

Table 7.5 Independent predictors of all-cause mortality over 5.25 years in people with newly diagnosed type 2 diabetes excluding 36 with missing data (n=700 (95.1%))

	Odds Ratio (OR)	95%CI	*P* value
Age	1.09	1.06, 1.12	<0.001
Cigarette Smoking	1.89	1.01 -3.54	0.048
Elevated Blood Pressure	1.93	1.08, 3.44	0.026
VPT >25v	2.22	1.31, 3.77	0.003
Proteinuria	1.95	1.02, 3.72	0.043
Townsend Quartiles	1.37	1.10, 1.70	0.005

Discussion

Duration of diagnosed diabetes is a possible confounding factor in mortality studies of diabetic populations. It is likely that diabetes duration will affect mortality trends both positively and negatively. On the one hand, duration is an independent risk factor for diabetic complications [139] and, on the other, increased duration may introduce a "survivor" effect, as well.

We have shown that even in an early phase of the disease process, namely when people are newly diagnosed, type 2 diabetes is associated with markedly adverse mortality outcomes. A substantially increased risk of death is demonstrated across all age groups. Mortality odds ratios for cardiovascular, malignancy-related, and other deaths approximately double when compared to a carefully selected local age and sex matched control population. Women with newly diagnosed type 2 diabetes and aged less than 75 years appear to be most affected and have mortality odds seven times that of a control population, in this cohort. However, even those cohort members aged 75 years and over have a doubling of the odds of death when compared to controls. We are unaware of any other studies that have reported on mortality in unselected populations with newly diagnosed type 2 diabetes.

We have clearly demonstrated the need for carefully selected comparator data in mortality studies. Using national mortality data, and after age and sex standardization, there is a considerable underestimate of the impact of type 2 diabetes on mortality. This is due to mortality rates in the local population being lower than that expected by extrapolating from national mortality statistics. We are aware of only one UK study of cause-specific mortality that has addressed

this issue by studying all people with diabetes in the area and using the entire local population, after age and gender stratification, as a comparator [140].

Diabetes is consistently underreported on death certificates [141-143]. This was the case in our study population with less than a third of the certificates containing a reference to diabetes. Furthermore, our data suggests that the underreporting applies to cardiovascular disease, as well. Cause-specific mortality results based on death certificates must be interpreted with caution, as these are dependent on both ICD coding rules and possible inconsistencies at the time of physician entry of mortality information.

In the absence of other reports of mortality in unselected populations with newly diagnosed type 2 diabetes, we are unable to provide a direct comparison. Furthermore, it is recognised that on an international level, the age structure of people with diabetes varies considerably and difference between reports related to the age bands used, hinders attempts at comparison. Our results for all-cause mortality are broadly similar to those seen in a previous study from the Poole area [9]. However, there are significant differences in relation to cause-specific mortality. We have shown an increase in cancer mortality and other non-cardiovascular causes (predominantly respiratory) that was not evident in the earlier study. A "survivor" effect in the earlier study would be a possible explanation. An increase in cancer deaths in people with type 2 diabetes has been reported in the past, but is an inconsistent finding [124,126,130-132]. The literature has conflicting reports from different countries on the impact of type 2 diabetes on mortality in people over the age of 75 years [9,125,144]. However, both our study and the previous mortality study from Poole demonstrate an adverse

impact of diabetes on mortality in this age group. It is unclear whether the difference in results relates to selection methods, the comparators chosen or differences in age structures and disease rates in the background populations.

Unlike the background population, after age-adjustment, gender does not predict all-cause mortality in people with newly diagnosed type 2 diabetes. The multivariate model clearly demonstrates the adverse impact of smoking, microvascular disease at diagnosis (in the form of peripheral neuropathy and proteinuria), elevated blood pressure, and socioeconomic deprivation on mortality risk. Although these risk factors have been described previously in individual reports, their combined burden has not been demonstrated in a population with type 2 diabetes. Smoking, proteinuria and elevated blood pressure are well-documented risk factors for mortality [145,146]. Neuropathy has been shown to predict mortality in people with diabetes [147] but the reasons for this are unclear. Due to limited numbers, we are unable to provide a robust explanation but there was a trend towards increased deaths from respiratory and cardiovascular disease. Deaths due to foot sepsis were not contributory. It is possible that the elevated vibration perception threshold is a surrogate marker for cardiac autonomic instability and increases the risk of death in susceptible individuals. This finding warrants further study. The Townsend score is one of several composite indices developed to measure geographical deprivation such as the Jarman index and Carstairs score. Previous studies have documented the increased mortality risk associated with deprivation [94,95]. Health behaviour, alcohol consumption, life stresses, access to health services, and other environmental factors may play a role. The results of the multivariate model

provides information that could help identify individuals at the time of diagnosis of type 2 diabetes who are likely to benefit from targeted, and possibly tailored, health improvement measures and also direct future health care research in this population.

We have studied all patients with newly diagnosed diabetes in a defined community. The results reflect usual clinical practice in both the hospital and primary care setting. There are limitations to the study. Predominantly, the modest cohort size restricts detailed comment on gender and cause-specific mortality and limits exploration of the age, gender, and cause-specific mortality trends underlying the predictors of mortality. We were unable to adjust for diagnosis of diabetes in the control population following enrolment in the study. However, we have previously reported an age/sex-adjusted annual incidence rate of newly diagnosed type 2 diabetes of 1.67/1000 (95%CI 1.49,1.84) in the same population [148]. Based on patient-years, 6-8 new diagnoses of diabetes in the control group during the study period would be expected and hence, our mortality odds ratios may marginally underestimate the true impact of type 2 diabetes. Limited information pertaining to lipids was available in those aged over 75 years and we were consequently unable to evaluate the impact of lipid fractions. The HbA_{1c} measurements relate to the time of diagnosis and do not represent glycaemic exposure over the course of the study. Nonetheless, our novel report lays the foundation for future research into mortality outcomes in people with a new diagnosis of type 2 diabetes.

In conclusion, newly diagnosed type 2 diabetes is associated with an approximate two-and-a- half-fold increase in the odds of mortality over the first

five years from diagnosis. The increase in odds is seen in all age groups and for all causes of mortality. A plausible implication of the study findings is that it may be too late to wait for a diagnosis of type 2 diabetes and that preventive policy need to be targeted based on diabetes risk. We have clearly shown that the increased mortality risk associated with type 2 diabetes exists, at the very least, from the time of diagnosis. Our report provides a foundation for future research into mortality outcomes and predictors of mortality, in people with a new diagnosis of type 2 diabetes.

CHAPTER 8

Proteinuria and calculated GFR as predictors of early mortality in people with newly diagnosed type 2 diabetes

Introduction

Chronic kidney disease (CKD) is known to increase cardiovascular and non-cardiovascular mortality both in people with and without diabetes [149-151]. Additionally, in people with diabetes, proteinuria per se is an independent predictor of all-cause mortality. A good portion of this excess in deaths relates to renal and cardiovascular causes [146,152,153].

Recently, and following a review of the available literature, the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) guidelines [154] recommended adoption of the newer Abbreviated MDRD (Modification of Diet in Renal Disease) equation [26] in preference to the Cockcroft-Gault (CG) equation [27] for derivation of an estimated glomerular filtration rate (eGFR). The MDRD study equation is believed to be more accurate and precise than the Cockcroft-Gault equation for persons with a GFR less than approximately 90 mL/min per 1.73 m^2 [26] and has been validated in a number of populations. However, the MDRD equation has not been validated in diabetic kidney disease and available reports have shown mixed results when its performance is compared to that of the Cockcroft equation [155-158]. The NKF K/DOQI do suggest that in clinical conditions associated with extremes of body size, severe malnutrition or obesity and rapidly changing kidney function, a clearance method may offer more useful results. It is useful to note that the original Cockcroft-Gault equation was designed to estimate creatinine clearance. Because of recent guidelines including the National Service Framework (NSF) for renal services [159], clinical laboratories in the United Kingdom and abroad are beginning to report eGFR values routinely on serum creatinine measurements.

A small prospective study in people with recently diagnosed type 2 diabetes reported that glomerular filtration rate (GFR) determined by isotopic methods (plasma clearance of 51 Cr^{-} EDTA) predicted all-cause mortality even at relatively normal values [160]. It is unclear whether Cockcroft-Gault or MDRD eGFR will add to the prediction of early mortality in people with a new diagnosis of type 2 diabetes, particularly in those identified to have mild to moderate reductions in GFR (equivalent to Stage 2/3 CKD or GFR <90ml/min and ≥30ml/min /1.73 m^2).

In the context of the above, we have studied the agreement in derived values of the two methods of estimating GFR and their ability to predict early mortality in people with newly diagnosed type 2 diabetes. We have also studied whether eGFR values add to the known predictive value of age, proteinuria and other risk factors for early mortality.

Study Methods

Study Participants

All 736 cohort members and their age/sex matched controls as described in **Chapter 2** were entered into this analysis.

Death registration

As in **Chapter 7.**

Design

As described in **Chapter 7**, data collection ended on September 30th, 2003 and mortality status determined for each individual at a time point of 5.25 years from study entry. This was the minimum completed follow-up period in the study for all survivors. Body surface area was estimated using the equation described by Mosteller RD et al [161]. Abbreviated four-variable MDRD GFR and Cockcroft-Gault GFR were calculated using the standard equations [26,27] (**See Appendix D**). Cockcroft-Gault GFR was adjusted for standard body surface area (1.73 m^2) as it differs from the MDRD equation in this respect. Treatment data was collected at the time of initial interview and by review of the computerised prescribing data in the general practices.

In view of the effects of therapy on baseline variables, blood pressure and lipids were treated as categorical variables as described in **Chapter 7.**

Statistical Analysis

Since GFR is known to fall with age, unadjusted and age-adjusted odds ratios were ascertained for both eGFR equations. A Bland-Altman plot [162] was used to assess the degree of bias and precision between the two methods of evaluating eGFR. The predictive value of both Cockcroft-Gault eGFR and MDRD eGFR for

mortality (all-cause and cardiovascular disease) were assessed by plotting receiver operating characteristic (ROC) curves [51] and calculating the area under the curve (AUC) along with 95% confidence intervals. Binary logistic regression was used to compute odds ratios in the multivariate analysis. Due to the limited numbers of expected deaths in the cohort, all-cause mortality was the only tested end-point.

Results

Baseline characteristics of people with newly diagnosed type 2 diabetes are described in **Table 8.1.**

There were 147 deaths recorded during the study. Of these, the underlying cause of death was cardiovascular (ICD9 codes 410-414) in 62 (42.2%). There were two deaths from renal causes (ICD9 codes 580-589)

The Bland-Altman plot showed a small degree of bias (mean 2.2 ml/min) but a significant lack of precision (2SD: -30.1 to +34.6 ml/min) between the two methods of eGFR calculation (**Fig. 8.1**). There is no evidence of a systematic bias in either of the methods but there is considerable scatter of individual values. A degree of non-linearity is evident with Cockcroft-Gault eGFR increasing disproportionately to MDRD values at higher levels of GFR. The lack of precision suggests that an individual has a substantial chance of being allocated to different CKD stages depending on the adopted GFR estimation method.

The receiver operating characteristic curves showed that the body surface area-adjusted Cockcroft-Gault eGFR had better discriminative value for all-cause mortality than the MDRD equation (**Fig. 8.2**). A reduction in GFR as estimated from the Cockcroft-Gault equation has a greater probability of identifying individuals who fail to survive when compared to the MDRD equation. The AUCs were 0.747 (95% CI 0.702 - 0.810) vs. 0.647 (95% CI 0.594 - 0.700); p=0.042. Similar values were seen for CVD death (0.737 (95% CI 0.679 - 0.789) vs. 0.663 (95% CI 0.601 - 0.724)) but failed to achieve statistical significance due to the smaller number of events (p=0.057).

CKD stages as identified by both eGFR methods were associated with a significant trend towards increasing mortality. However, a clearer demarcation of mortality odds (particularly for Stage 2 CKD or GFR 60-89 ml/min) was seen with the Cockcroft-Gault method. The correlation coefficient of CG eGFR and age was significantly higher than that of MDRD eGFR and age (-0.84 and -0.52, respectively) and after adjusting for the effect of age on mortality, Stage 2 and Stage 3 Chronic Kidney Disease (GFR <90ml/min and ≥30 ml/min) as determined by either eGFR method was not associated with an increase in mortality odds **(Table 8.2)**. Proteinuria was associated with an approximately 2.5-fold increase in mortality odds prior to adjustment for age and a two-fold increase following adjustment.

In the multivariate model, proteinuria, cigarette smoking, elevated blood pressure, and age were associated with a greater risk of death (**Table 8.3**). Besides for age at diagnosis, these covariates were associated with an approximate doubling of the mortality odds ratio. MDRD eGFR and Cockcroft-Gault eGFR did not appear to be independent predictors of early mortality with associated odds ratios approaching unity.

Table 8.1 Baseline characteristics of the 736 participants with type 2 diabetes in the study

	Missing (n)	Mean (±SD) or n(%)
Age (years)	0	64.3 (±13.3)
HbA_{1C} (%) at diagnosis	4	10.4 (±2.8)
Gender - Males	0	403 (54.8%)
BMI at diagnosis (kg/m^2)	6	30.2 (±6.6)
Elevated Blood Pressure	17	524 (72.9%)
Elevated Cholesterol	20	556 (77.7%)
Elevated Triglyceride	20	462 (64.5%)
Smokers	0	111 (15.1%)
Proteinuria	2	70 (9.5%)
MDRD eGFR	5	74.6 (±17.6)
Cockcroft- Gault eGFR	9	76.8(±27.4)

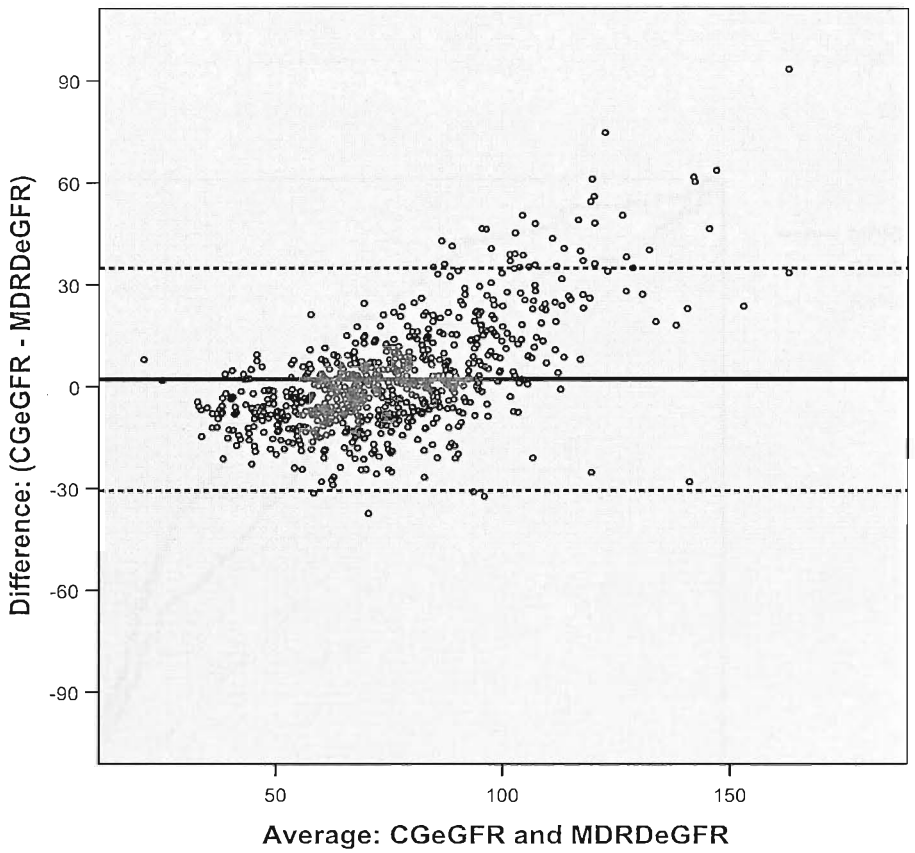
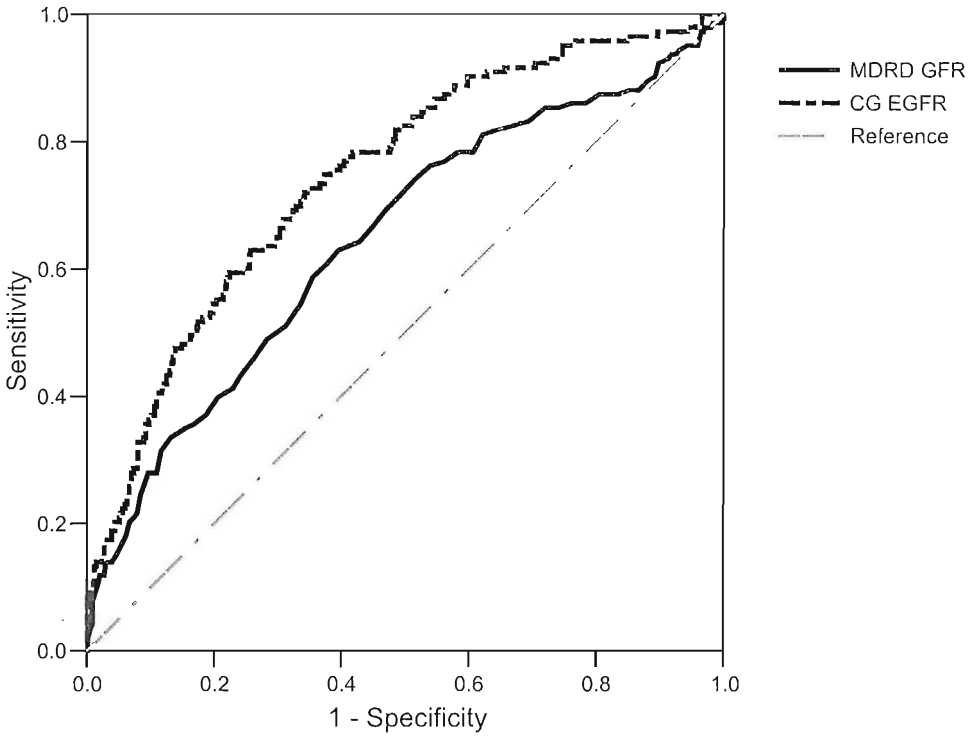


Fig.8.1 Bland-Altman plot of CG eGFR and MDRD eGFR at baseline. Mean difference (bias) and 95% confidence intervals (precision) are indicated by the intact and broken lines, respectively.



	Area under the curve AUC; 95% CI
MDRD GFR	0.647; 0.594 - 0.700
Cockcroft - Gault GFR	0.747;0.702 - 0.810

MDRD vs, Cockcroft- Gault GFR area under the curve; p=0.042

Fig.8.2 Receiver operating characteristics (ROC) curves evaluating the discriminative ability of MDRD GFR and body surface area adjusted Cockcroft-Gault GFR for all-cause mortality in people with newly diagnosed type 2 diabetes over 5.25 years.

Table 8.2 Odds ratios for all-cause mortality in people with newly diagnosed type 2 diabetes according to MDRD and Cockcroft-Gault derived CKD stage and for proteinuria alone, before and after age-adjustment.

	N (%)	Unadjusted Odds Ratio (95% CI)	*P*	Age- adjusted Odds Ratio (95% CI)	*P*
MDRD eGFR			<0.001 [a]		0.081 [a]
GFR ≥ 90ml/min	128 (17.4)	1.00		1.00	
GFR 60-89 ml/min	458 (62.2)	1.14 (0.66 - 1.97)	0.635	0.42 (0.22 -0.79)	0.007
GFR 30-59 ml/min	143 (19.4)	3.08 (1.70 -5.60)	<0.001	0.49 (0.23 -1.03)	0.058
GFR <30 ml/min	2 (0.3)	5.74 (0.34 - 95.7)	0.224	3.77 (0.18 -79.24)	0.393
Cockcroft-Gault eGFR			<0.001 [a]		0.231 [a]
GFR ≥ 90ml/min	187 (25.4)	1.00		1.00	
GFR 60-89 ml/min	338 (45.9)	2.65 (1.38 -5.11)	0.004	0.63 (0.29 - 1.35)	0.230
GFR 30-59 ml/min	197 (26.8)	8.96 (4.67 - 17.20)	<0.001	0.68 (0.27 -1.74)	0.423
GFR <30 ml/min	5 (0.7)	58.33 (6.04-563.51)	<0.001	6.72 (0.42 -107.11)	0.177
Proteinuria	70 (9.5)	2.66 (1.58-4.49)	<0.001	1.90 (1.06 - 3.43)	0.032

[a] Jonckheere-Terpestra test for trend
Odds Ratio v. GFR≥90ml/min.

Table 8.3 Predictors of all-cause mortality over 5.25 years in people with newly diagnosed type 2 diabetes excluding 36 with missing data (n=700 (95.1%)) utilising both MDRD and body surface area-adjusted Cockcroft-Gault methods to estimate GFR.

	Cockcroft-Gault eGFR			MDRD eGFR		
	Odds Ratio (OR)	95%CI	*P*	Odds Ratio (OR)	95%CI	*P*
Age	1.10	1.06, 1.14	<0.001	1.10	1.07, 1.13	<0.001
Cigarette Smoking	2.07	1.11, 3.85	0.048	2.06	1.10, 3.83	0.023
Elevated Blood Pressure	1.81	1.03, 3.19	0.040	1.80	1.02, 3.17	0.043
Proteinuria	2.06	1.09, 3.90	0.026	2.09	1.10, 3.95	0.024
Female Gender	0.99	0.63, 1.54	0.957	0.99	0.63, 1.56	0.974
HbA_{1c} at diagnosis	0.94	0.87, 1.01	0.111	0.94	0.88, 1.02	0.115
Elevated total cholesterol	1.15	0.67, 1.98	0.609	1.15	0.67, 1.98	0.609
Elevated triglycerides	1.05	0.66, 1.68	0.831	1.05	0.66, 1.67	0.848
Body Mass Index	1.00	0.95, 1.05	0.863	1.00	0.95, 1.04	0.773
eGFR	1.00	0.98, 1.02	0.830	1.00	0.99, 1.02	0.968

Discussion

Increasing urinary albumin excretion is associated with an increase in mortality rates [163,164]. This may reflect a direct impact of albumin excretion on cardiovascular mortality or may be a marker for adverse risk profiles linked to factors like increased platelet aggregability, autonomic neuropathy and endothelial dysfunction [165,166]. The actual prevalence of proteinuria in people with type 2 diabetes has been reported in cross-sectional studies to range from 5% [167] to 19% [168]. Some of this variation may relate to differences in urine collection methods, ethnicity, definition of proteinuria, and duration of diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) suggested that at diagnosis of type 2 diabetes, the prevalence of proteinuria was 1.9% [32]. The higher prevalence rates seen in our study are likely explained by the age, diagnostic and exclusion criteria applied to the UKPDS cohort that is dissimilar to our study population.

Progression of renal disease from proteinuria to ESRF in people with diabetes occurs after approximately 10 years [164]. It is self-evident that untreated end-stage renal failure (ESRF) is universally fatal. Hence, mortality reports largely relate to people on dialysis or those who are post-transplantation. Once on dialysis, patients with diabetes have significantly higher mortality rates when compared to those without diabetes. The UKPDS patients on dialysis had a one-year survival of 79.5% [164]. Vascular disease underlies a significant portion of the increased deaths and infection is the second largest cause of mortality in patients on dialysis. The increase in cardiovascular mortality is unsurprising as clinically apparent coronary artery disease is present in 40% of people with ESRF

[169] and left ventricular hypertrophy is present in 75% on initiation of dialysis [170]. Although significantly elevated serum creatinine levels (>150μmol/l) have been shown to be a predictor of mortality in people with type 2 diabetes [140], it is unclear whether this applies to mild or moderate reductions in the glomerular filtration rate and whether this is independent of the impact of proteinuria and other traditional risk factors, including age. Since calculated GFR measurements are becoming part of the data collected in diabetes clinics, this question is of particular importance and the clinical relevance and prognostic impact of abnormal GFR values identified by the equations needs to be explored. Ideally, a clear understanding of the clinical utility should precede widespread adoption of the clinical measurement as part of routine diabetes healthcare delivery.

Our results show that in people with type 2 diabetes, individual GFR results calculated by the Cockcroft-Gault and the abbreviated MDRD equations can vary widely. In terms of clinical utility, staging of an individual's renal disease will depend on the method adopted and this variation is likely to have a "knock-on" effect in terms of therapeutic and clinical management choices.

We have shown that body surface area-adjusted Cockcroft-Gault eGFR has modestly improved predictive value for all-cause mortality in people with a new diagnosis of type 2 diabetes as compared to the Abbreviated MDRD equation and that the two methods have poor precision when compared to one another. However, neither method predicts mortality in people with early CKD (Stage 2 and Stage 3) when the impact of age is taken into account. Proteinuria, unlike eGFR, remains a powerful and independent predictor of early mortality in this population.

We have not evaluated renal outcomes as an endpoint and hence we are unable to comment on the utility of these equations as indicators of worsening renal function in people with type 2 diabetes. Nonetheless, our results lend weight to the argument that widespread adoption of either MDRD or Cockcroft-Gault methods to estimate GFR in people with type 2 diabetes should be preceded by careful validation studies and a more complete exploration of the clinical utility of these measurements in the diabetes clinic setting.

We have studied all patients with a new diagnosis of type 2 diabetes in a well-defined population. The presence of proteinuria was confirmed on a second specimen after a period of several months to exclude transient proteinuria. Since we have not used a quantitative measure of protein excretion, we are unable to comment on the impact of increasing albumin excretion on mortality. Our results do reflect usual clinical practice in the United Kingdom. In our study, creatinine was estimated using a modified Jaffe method and this is known to overestimate creatinine levels. However, creatinine assays are yet to be standardised in the United Kingdom and the method used is widely adopted in laboratories across the country. The impact of the different assays on the GFR equations is the subject of an ongoing debate [171].

In conclusion, proteinuria, which is an easily accessible clinical measurement in the diabetes clinic setting is a robust marker of increased mortality odds and identifies individuals who may benefit from targeted therapeutic intervention. Mild to moderate reductions in GFR identified using standardised equations in people with newly diagnosed type 2 diabetes do not independently add to the risk of early mortality. It is evident that calculated

measures of glomerular filtration rates may complement, but must not supplant urine protein estimation in the diabetes clinic setting.

CHAPTER 9

Conclusion

This study reports cardiovascular and mortality outcomes in a community-based cohort of people with a new diagnosis of type 2 diabetes. Such data is scarcely found in the medical literature and is essential for effective prognostication and management of people who are diagnosed with type 2 diabetes.

I have shown that the annual incidence of diagnosed type 2 diabetes in the Poole area is 1.93/1000 individuals. Applying this figure to the demographics of the UK population, I estimate an annual incidence of 98,000 or around 300 cases diagnosed each day. This information is essential to the planning of local health delivery and assessment of health needs. Furthermore, I have provided comparator data for similar studies in different geographical regions of the United Kingdom and in other countries. Re-studying incidence and prevalence rates of diagnosed type 2 diabetes in the future, will allow modelling of the drivers underpinning the increasing prevalence of diagnosed type 2 diabetes.

I have evaluated the performance of the Framingham cardiovascular and coronary heart disease risk model and the UKPDS risk engine for coronary heart disease in a population with newly diagnosed type 2 diabetes. Both calculators suffer from modest discrimination and are poorly calibrated and are less than ideal tools for the prediction of incident cardiovascular disease in people with diabetes. I have shown that the metabolic syndrome is associated with a twofold hazard of incident cardiovascular disease and disease-free survival incrementally and progressively worsens with the number of features of the metabolic syndrome that are present. These results suggest that the metabolic syndrome features may be useful markers of vascular outcomes even in people with type 2

diabetes and may be a useful therapeutic target, as well. I have shown that material deprivation independently predicts incident cardiovascular disease in people with type 2 diabetes beyond the risk conferred by the metabolic syndrome and traditional risk calculators.

I hope that my results will underpin and inform development of risk prediction tools specifically for people with diabetes. My firm belief is that a "risk-based" therapeutic strategy is in the best interests of the health service and the individual patient with diabetes. It is particularly important that we develop effective clinical tools for this purpose. In particular, the link between deprivation and cardiovascular disease needs to be closely explored as this seems to explain a significant portion of the failure of contemporary vascular risk scoring methods to effectively quantify risk. The development of a validated, effective clinical definition of individual deprivation is a priority. Furthermore, the impact of ethnicity in the setting of vascular risk assessment in people with newly diagnosed type 2 diabetes needs to be studied. Multifactorial risk assessment using a broad spectrum of variables linked to cardiovascular disease is likely to provide the highest predictive value (although over-complexity will cause problems, too). A staged risk assessment structure using demographic and metabolic parameters followed by vascular imaging techniques for "next-step" risk stratification in sub-populations would be an approach worth modelling. Future developments in genomics (Diabetes Genome Anatomy Project [www.genome.org]) may well inform risk stratification measures.

I have shown that even in the early stages of the disease, following diagnosis, people with type 2 diabetes face a substantially increased mortality burden. Even the elderly are adversely affected and women have a drastic threefold increase in their mortality odds. Once again, material deprivation is a prominent factor which we first need to understand and then therapeutically target so as to shrink social iniquity in health.

The work on calculated GFR not only provides data on the lack of association between mild to moderate reductions in calculated glomerular filtration rate and mortality outcomes, and the continuing need to evaluate urine protein excretion as a renal marker of adverse outcomes in diabetes: it also underlines the need to understand the implications of a clinical measurement prior to its adoption in the routine clinical process.

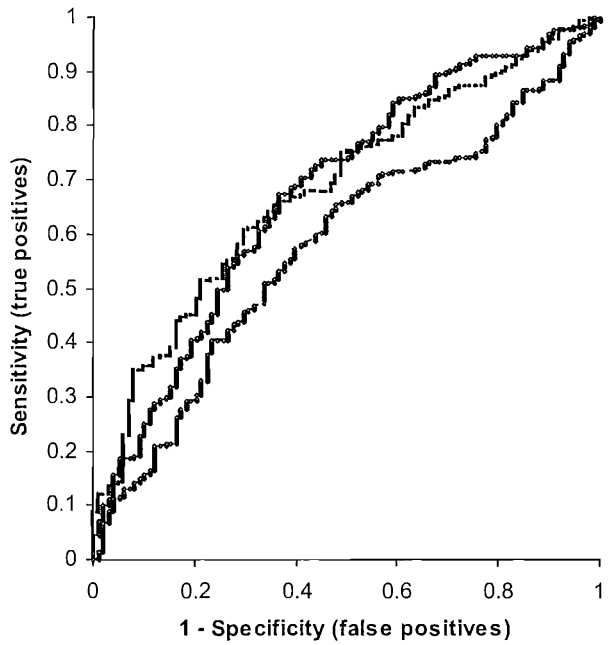
I hope that by defining disease burden, particularly cardiovascular and mortality outcomes and the predictors of these outcomes in people with newly diagnosed type 2 diabetes, this and future studies will help establish the basis for intervention trials and the development of clinical services for individuals who develop type 2 diabetes.

APPENDIX A: RECEIVER OPERATING CHARACTERISTIC CURVES

Receiver operating characteristic (ROC) curve analysis originated as part of a field known as "Signal Detection Theory" which was developed in World War 2 to analyse radar images. Since radar operators had to decide whether a "blip" on the screen represented an enemy or a friendly vessel, or even interference, this tool was developed. Signal detection theory plots the probability of the origin of the "blip" based on the measured characteristics of the signal. Hence, the term adopted was Receiver Operating Characteristics.

It was not until the 1970's that signal detection theory was recognized as useful for interpreting medical test results.

In essence, an ROC curve is a graphical representation of the trade-off between the false positive and true positive rate for every cut-off point of a continuous variable tested against a dichotomous outcome measure. It is a measure of the accuracy of the test.



An ROC curve is simple to construct. The event/outcome that is being measured must be discrete and dichotomous; an example would be mortality as an outcome. The test variable is usually continuous; an example would be age. For every value of the test variable seen in the population studied the false positive rate (1-specificity) and the true positive rate (sensitivity) is calculated. This is then plotted on a graph with the false-positive rate on the x-axis and the true positive rate on the y-axis. It is possible to plot curves for several continuous variables (with the same dichotomous outcome measure) on the same graph to allow comparison (as shown in the preceding example).

Several features may be assessed from an ROC curve - 1) The trade-off between sensitivity and specificity is easy to visually assess 2) The slope of the tangent at any point on the curve gives the likelihood ratio at that value of the continuous variable tested 3) Finally, the closer the curve hugs the left and then upper border of the graph margins, the more accurate the test and the closer the curve lies to the diagonal line, the less accurate the test. This is best assessed by the calculating the area under the curve (the proportion of the box lying below the curve and the x-axis) using a computer programme. The non-parametric approach is often used. The area under the curve can range from 0.5 (the diagonal line) to 1.0. This area is a measure of the "discrimination" of the test. Discrimination relates to the ability of the test to classify people as "affected" or "unaffected" based on the dichotomous variable. A test with an area under the curve of 0.5 is worthless and equivalent to a coin-toss whereas a test with an area of 1.0 is 100% accurate. In practice, most results fall

somewhere between. A value of more than 0.8 is good, and one above 0.7 is fairly accurate.

APPENDIX B: MODIFIED HOSMER-LEMESHOW x^2 STATISTIC

The Hosmer-Lemshow x^2 statistic is a goodness-of-fit test. Goodness-of-fit tests examine the difference between the observed and expected outcomes in a group of individuals based on a predictive model. This is a measure of "calibration". Calibration evaluates the degree of correspondence between the estimated probabilities of an outcome from a model and the actual outcomes observed.

The unmodified Hosmer-Lemshow x^2 test divide patients into ten groups containing approximately 10% of the studied cohort. TheHosmer-Lemshow x^2 statistic is calculated and then compared to a chi-square distribution and a P value can be derived. If the P value is large, the model is well calibrated and if small, the calibration is poor.

The modified Hosmer-Lemshow x^2 test is used where the outcome is relatively rare. Rather, than split the population into ten equal groups, the population is ranked according to their risk probability and then split into ten groups such that the expected number of events in each group is equal. The Hosmer-Lemshow x^2 statistic is compared to a chi-square distribution as in the unmodified test with 8 degrees of freedom. Small Hosmer-Lemshow x^2 values (less than 15) indicate good calibration.

APPENDIX C: TOWNSEND DEPRIVATION SCORE

The Townsend Score is a measure of the levels of material deprivation. It comprises of four variables:

1. Unemployment (lack of material resources and insecurity)
2. Overcrowding (material living conditions),
3. Lack of owner occupied accommodation (a proxy indicator of wealth)
4. Lack of car ownership (a proxy indicator of income).

The Townsend Score is a summation of the standardised scores (z scores) for each variable (scores greater than zero indicate greater levels of material deprivation). The z score is simply the 'observation' (percentage or proportion for the ward on a given measure) minus the mean observation divided by the standard deviation (for England & Wales).

Individual postcode data can be linked to ward Townsend scores to derive geographical deprivation data. A higher Townsend score indicates greater material deprivation.

Other commonly used indices of material deprivation are the DoE, Jarman, and Carstairs scores.

The Townsend score is considered to be one of the best indicators of material deprivation currently available.

APPENDIX D: EQUATIONS USED IN THE STUDY

Friedwald's equation to calculate LDL cholesterol

LDLc (mmol/l) = TC - HDLc - (TG/2.2)

LDLc = LDL cholesterol; TC = total cholesterol; HDLc = HDL cholestesterol;

TG = triglycerides *(all in mmol/l)*

Framingham model for 10 year coronary heart disease risk

	Men	Women	Input Range
Gender (V1)	+11.1122	+ 5.2573	
Age (V2)	- 1.4792 x log(age)	+ 1.8515 x $(\log(age/74))^2$	30-74 years
TC/HDL ratio (V3)	- 0.7181 x log(TC/HDL)	- 0.7181 x log(TC/HDL)	
Systolic BP (V4)	- 0.9119 x log(SBP)	- 0.9119 x log(SBP)	
Smoking status (V5)	- 0.2767 x Smoking	- 0.2767 x Smoking	Non-smoker=0 Smoker=1
Diabetes (V6)	- 0.1759 x DM	- 0.3758 x DM	DM no=0, yes=1
LVH on ECG (V7)	- 0.5865 x LVH	- 0.5865 x LVH	LVH no=0, yes=1

$$X1 = V1 + V2 + V3 + V4 + V5 + V6 + V7$$

$$X2 = (-2.1155149 - X1) / \exp(-0.3155 - (0.2784 \times X1))$$

The probability for CHD (in %) within 10 years is
$P = 100 \times (1-\exp(-\exp(X2)))$

TC/HDL= total cholesterol/HDL cholesterol ratio; SBP = systolic blood pressure;

LVH = left ventricular hypertrophy; ECG = electrocardiogram

UKPDS risk engine score for 10-year coronary heart disease

$q0$ = Intercept = 0.0112

$b1$ = Risk ratio for one year of age at diagnosis of diabetes = 1.059

$b2$ = Risk ratio for female sex = 0.525

$b3$ = Risk ratio for Afro-Caribbean ethnicity = 0.390

$b4$ = Risk ratio for smoking = 1.350

$b5$ = Risk ratio for 1% increase in HbA_{1c} = 1.183

$b6$ = Risk ratio for 10 mmHg increase in systolic blood pressure = 1.088

$b7$ = Risk ratio for unit increase in logarithm of lipid ratio (TC/HDL) = 3.845

d = Risk ratio for each year increase in duration of diagnosed diabetes = 1.078

$q = q0 \times b1^{age-55} \times b2 \times b3 \times b4 \times b5^{HbA1c-6.72} \times b6^{(SBP-137.5)/10} \times b7^{ln(TC/HDL)-1.59}$

10 year CHD Risk (R) = $1-exp\{-q[(1-d^{10})/(1-d)]\}$

Cockcroft-Gault equation for creatinine clearance

CGeGFR in men (ml/min) = 1.23 x weight (kg) x (140 - age (years)) / Creatinine (μmol/l)

CGeGFR in women (ml/min) = 1.03 x weight (kg) x (140 - age (years)) / Creatinine (μmol/l)

Abbreviated MDRD equation for calculated glomerular filtration rate

MDRD eGFR = $186 \times ([\text{Creatinine (μmol/l)} / 88.4]^{-1.154}) \times (\text{age(years)})^{-0.203} \times$ (0.742 if female) × (1.210 if African-American)

Body surface area calculation

BSA = $W^{0.425} \times H^{0.725} \times 0.007184/1.73$

BSA = body surface area (m2), W = weight (kg), H = height (cm)

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