Use of routinely collected data to assess outcomes in people with diabetes

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This thesis represents the culmination of many years work and it would not have been possible without the help and support of a wide range of people and organisations along the way.

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Foreword

The journey that has culminated in this thesis has been rewarding and interesting. I graduated from the University of York with a BA(Hons) in Social Policy. Whilst working in public health in Bradford I completed an MSc in Health Services Research at the University of York. My interest in the field of diabetes started when I undertook a year-long secondment to the Yorkshire and Humber Public Health Observatory, co-hosted by the Yorkshire and the Humber Strategic Health Authority and the University of York. This involved developing data tools and resources to assist service improvement in diabetes care across England. Overtime the scope of this role developed to include national and international projects to explore and develop data on people with diabetes and the healthcare services they require. Organisational changes, in particular, the move of the Public Health Observatories into Public Health England in 2013 meant that the scope for novel work and addressing research questions was restricted. Registering for a PhD gave me the chance to develop my research skills and pursue opportunities to use the large, routinely collated datasets, which I had become familiar with to focus on research questions.

The initial prompt for the analyses presented in this thesis varies due to restriction on the use of NDA data in early years so I therefore had to be nimble and seek out other opportunities. The analysis of mortality among inpatients with diabetes presented in Chapter 3 arose following concerns raised by Dr Rowan Hillson, then National Clinical Director for Diabetes. Chapter 4 is the result of a project set up by NHS Diabetes to explore the potential to collect and analyse data on the characteristics and outcomes of people with diabetic foot disease. Chapter 5 was a collaboration with Dr Bob Young and colleagues in Salford to explore a dataset that had been accumulated over a decade. Chapter 6 follows conversations with Dr Roger Gadsby and Dr Bob Young about the lack of evidence around the NICE recommendation for all people with diabetes to undergo nine clinical checks, known as care processes, on at least an annual basis as part of a review of the on-going management of diabetes and associated risks. Chapters 7 and 8 followed on from direct conversations with my supervisors and other colleagues around the emerging evidence of poor long-

term outcomes for people diagnosed with Type 2 diabetes in early adulthood with a particular reference to differences by ethnic group.

In all the analyses presented, I refined the research questions following conversations with clinical and other colleagues, and with approval of my supervisors. I explored the scope of the available datasets to address the question and developed specific hypotheses. I defined the data required and specified the statistical methods. I undertook the data preparation, cleaning and analysis. Initial findings were shared with co-authors and supervisors and, if required, the analysis was refined. Where the work has been published in peer reviewed journals I drafted the initial paper and co-ordinated editing and amendments with co-authors. I also managed the submission process to the journal, amended the paper following review in consultation with co-authors and drafted the response to reviewer comments. The chapters that have not yet been published in a peer-reviewed journal were fully drafted by myself and revised following comments from my supervisors. I am currently preparing some of the later chapters for submission to peer reviewed journals.

Since October of 2019, I have been fortunate to receive research funding from Diabetes UK to continue to explore the further use of the National Diabetes Audit to address research questions. Given the size of the National Diabetes Audit, this is a wonderful opportunity. This post will allow me the opportunity to build on the skills and knowledge I acquired during my PhD studies and to continue conversations and exploratory analysis to shed further light (and raise more questions) on outcomes of people with diabetes in a real world setting. It will also, hopefully, develop understanding of the scope and potential of the dataset and facilitate its use within the research community.

Summary

Current diabetes management is strongly influenced by a number of landmark trials that have highlighted the role of intensive blood glucose management and reduction of cardiovascular risk factors in reducing diabetic complications and ultimately the long term risk of mortality. This thesis collates contemporary data on aspects of diabetes care and diabetes outcomes in England and Wales and discusses the implications.

Analysis of data for inpatient stays across England shows that people with diabetes are disproportionately likely to die during their hospital admission compared to people without diabetes of a similar age. This can partly, but not wholly, be explained by a higher proportion of emergency admissions and reported co-morbidities. The additional risk of death associated with diabetes was significantly greater in smaller hospitals.

Having diabetes increases the risk of macro and micro vascular disease which can lead to poor foot health. Analysis of data collected over a twelve year period on all people presenting with diabetic foot ulcers in Salford, England highlights the significant morbidity and mortality in this group. Only 45% of ulcers had healed within 90 days and almost a fifth of people die within two years of presentation. The lack of nationally collated data on foot health meant that there was a significant gap in the knowledge of outcomes among people with diabetic foot disease. Designing a dataset and collection process, which was tested in 23 units across England, has led to the establishment of the National Diabetes Footcare Audit which now reports annually.

In an analysis of National Diabetes Audit data the recording of care processes and associated interaction with healthcare professionals appears to be associated with a lower risk of mortality than among people with diabetes for whom such care is not recorded.

Type 2 diabetes is increasingly being diagnosed at younger ages including early adulthood. Analysis of the National Diabetes Audit shows that people diagnosed with Type 2 diabetes aged between 20 and 39 years old have higher (age

adjusted) mortality than those diagnosed in later life. This is partly explained by higher prevalence of poorer cardiovascular risk factors but the additional relative risk remains statistically and clinically significant. The analysis also suggests that the increased relative mortality risk associated with diabetes in early onset Type 2 diabetes is present for White and Black ethnic groups but not for South Asians. Type 1 diabetes has traditionally been considered to result in a higher risk of cardiovascular events and death than Type 2 diabetes. However, if diagnosed in early adulthood medium term mortality risk is similar in people with Type 1 and Type 2 diabetes.

The work presented here provides an insight into the current outcomes of people with diabetes in England. It also illustrates the value of routinely collated datasets in building knowledge and identifies some of the challenges this type of analysis faces.

Peer reviewed publications and conference presentations

Peer reviewed publications of work presented in this thesis

Holman N, Young B, Stephens H, Jeffcoate W Pilot study to assess measures to be used in the prospective management of foot ulcers in people with diabetes *Diabetic Medicine* 2015:32(1) pp78-84

Holman N, Hillson R, Young RJ Excess mortality during hospital stays among patients with recorded diabetes compared to those without diabetes *Diabetic Medicine* 2013:30(12) pp1393-1402

Peer reviewed conference presentations of work presented in this thesis

Holman N, Sattar N, Wild S, Khunti K, Young B. Early onset Type 2 diabetes is associated with higher risk of mortality - An analysis of the National Diabetes Audit Oral and poster presentation at Diabetes UK Annual Professional Conference 2018, London

Holman N, Chadwick P, McAdam J, Haycocks S, Young B Longitudinal cohort of people presenting with diabetic foot ulcers in northern England Poster presentation at EASD Annual Meeting 2014, Vienna

Holman N, Chadwick P, McAdam J, Haycocks S, Young B Do ulcer characteristics and cardiovascular risk factors predict healing and mortality in people with diabetic foot ulcers in northern England? Poster presentation at EASD Annual Meeting 2015, Stockholm

Chapter 1: Introduction

Diabetes in the UK

Diabetes mellitus is defined by chronic hyperglycaemia due to an absolute or relative lack of insulin. The lack of insulin is due to the dysfunction or destruction of beta cells and therefore an inability to produce enough insulin for the body's needs. There are two main types of diabetes. Type 1 diabetes is an auto-immune disease resulting in the destruction of the insulin producing beta cells of the islets of Langerhans in the pancreas. This results in absolute insulin deficiency and is fatal without the regular administration of insulin to meet the body's requirements. Type 2 diabetes occurs when the pancreas is unable to produce sufficient insulin for the body's requirements. This may be the result of impaired insulin secretion and/or resistance to the action of insulin.

The symptoms of diabetes include frequent urination, especially at night, being thirsty, fatigue, unintentional weight loss, genital itching and thrush, cuts and wounds taking longer to heal and blurred vision. Type 1 diabetes is relatively fast in onset and, if untreated, diabetic ketoacidosis will develop and may be fatal. Type 2 diabetes is more gradual in onset and may be asymptomatic for many years.

Diagnostic criteria

There are currently three diagnostic criteria for diabetes and only one criteria needs to be met for a diagnosis to be made [1]. The criteria are

- A fasting plasma glucose of 7.0 mmol/l or greater
- A two hour post-load plasma glucose of 11.1 mmol/l or greater
- A HbA1c of 48 mmol/mol or greater

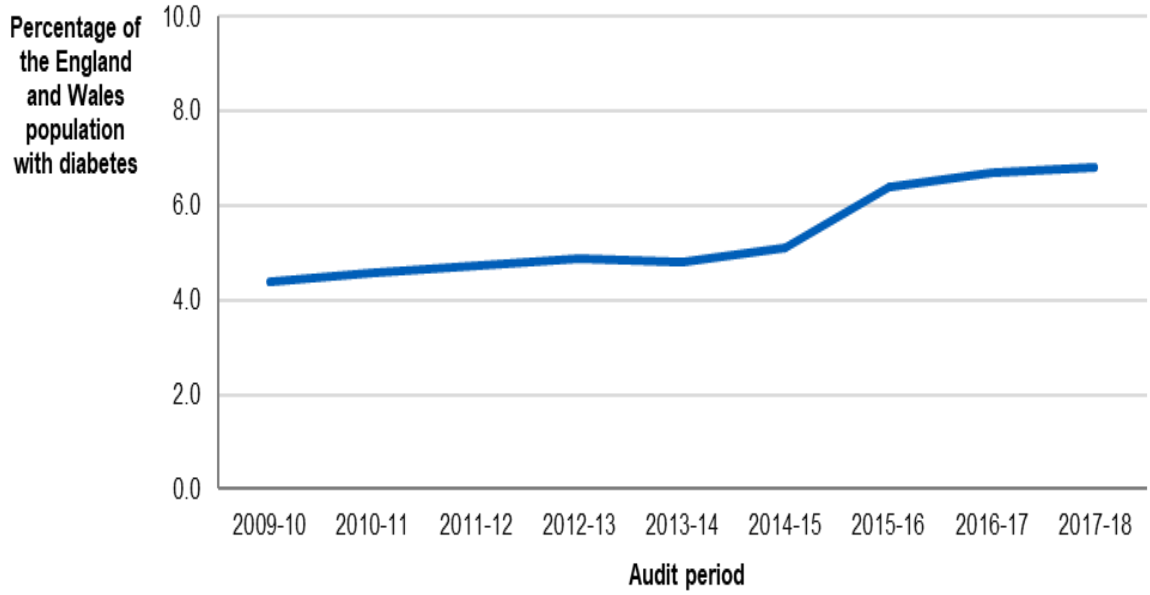
Current guidelines in the UK suggest that in an asymptomatic person the diagnosis of diabetes should never be based on a single raised HbA1c or fasting plasma glucose level and at least one further abnormal result should be obtained prior to formal diagnosis. In a symptomatic person a diagnosis of diabetes can be based on a single raised HbA1c or fasting plasma glucose measurement although it should be noted that severe hyperglycaemia in people with acute infection, trauma or circulatory stress may be transitory [2].

The World Health Organisation recommends the use of fasting plasma glucose to diagnose diabetes but acknowledges that HbA1c may also be used [3]. The European Association for the Study of Diabetes recommends that diagnosis of diabetes is made using either a fasting plasma glucose or HbA1c [4]. Similarly the American Diabetes Association recommends the use of HbA1c for the diagnosis of diabetes [5]. The use of HbA1c as a diagnostic test is practically simpler and does not require either a fasting prior to taking a blood sample or a glucose challenge with associated two hour wait for final blood samples. It can therefore be conducted anytime of the day and during acute illness such as after a myocardial infarction.

Diabetes Prevalence

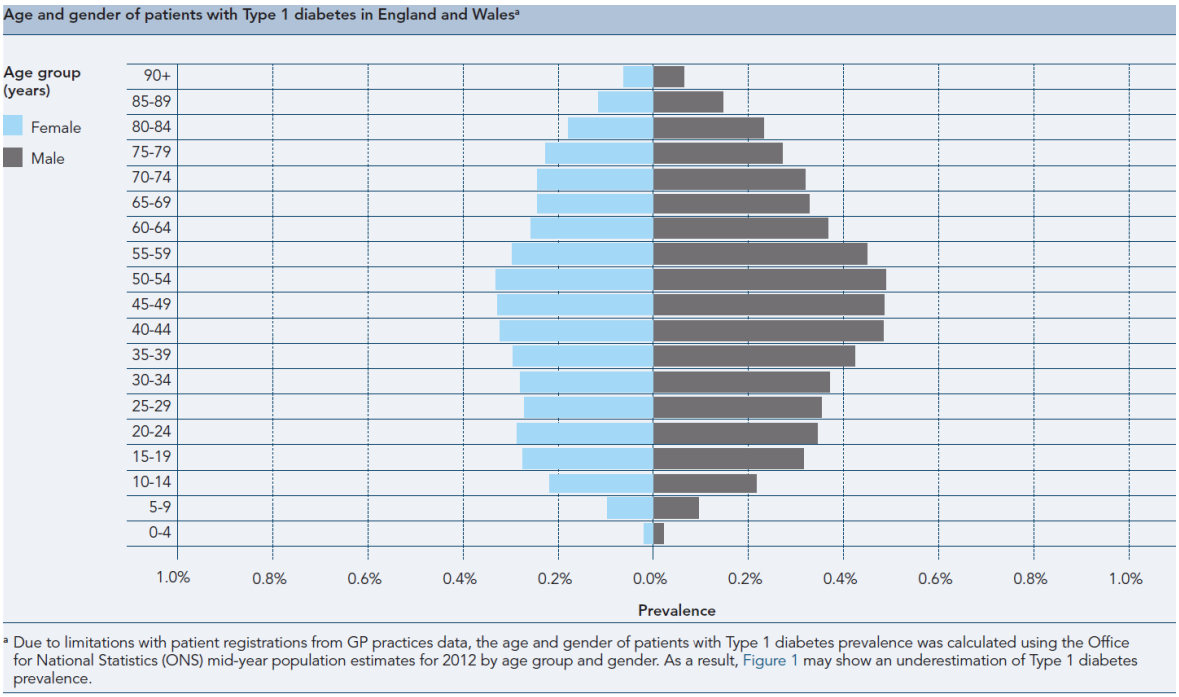
In England there are two main sources of data on the population prevalence of diagnosed diabetes. The Quality and Outcomes Framework is a set of quality assessment indicators linked to financial incentives for general practices [6]. As part of this general practices are required to maintain a register of all people aged 17 years and older with a diagnosis of diabetes (except gestational diabetes). These data show that the number of adults registered with a general practice in England with a diagnosis of diabetes has increased from 2,455,937 in 2011 [7] to 3,319,266 in 2019 [8]. The National Diabetes Audit also provides information on the current prevalence of diabetes in England and Wales and shows a similar increase in the prevalence of diagnosed diabetes over the same time period with 3,398,470 people of all ages being identified across England and Wales using data from primary care and specialist diabetes services (see **Figure 1.1**).

Figure 1.1 Prevalence of diabetes recorded by the National Diabetes Audit for England and Wales



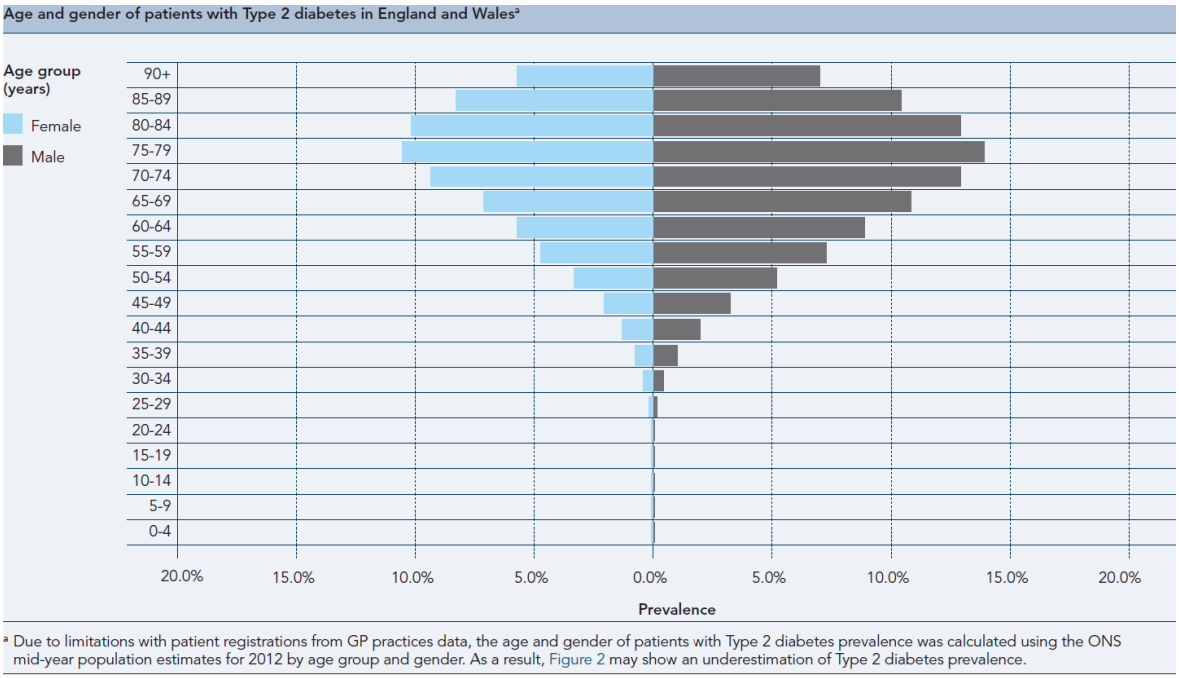
As the physiological mechanism underlying Type 1 diabetes is distinct from that related to type 2 diabetes there are significant differences in the epidemiology of the two most common types of diabetes. The age profile of people with type 1 diabetes is somewhat similar to that found in the general population (see **Figure 1.2a**). The prevalence of Type 1 diabetes is also higher amongst males than females across all ages. There is minimal evidence of an association between the prevalence of Type 1 diabetes and social deprivation. In the 2012/13 audit cohort 20.5% of people with Type 1 diabetes lived in the most deprived fifth of neighbourhoods compared to 18.9% living in the least deprived areas [9].

Figure 1.2a: Age and sex profile of people with Type 1 diabetes from the National Diabetes Audit, 2012/13



The epidemiology of Type 2 diabetes shows that risk is not evenly distributed across the population. The age profile of those diagnosed with Type 2 diabetes and included in the National Diabetes Audit for England and Wales show that the proportion of people diagnosed under the age of 40 years is low. The prevalence of Type 2 diabetes increases steadily up to the age of 80 years old. Declines in the prevalence of Type 2 diabetes after the age of 80 years can be attributed to the adverse impact of Type 2 diabetes on mortality and reduced life expectancy amongst those with the condition. Another explanation for a lower prevalence in type 2 diabetes above 80 years is that more people will be losing weight due other illness causing unintentional weight loss. This epidemiological phenomena is known as reverse causality. The prevalence of Type 2 diabetes is also higher amongst males than female at all ages (see **Figure 1.2b**).

Figure 1.2b: Age and sex profile of people with Type 2 diabetes from the National Diabetes Audit, 2012/13



Role of adiposity

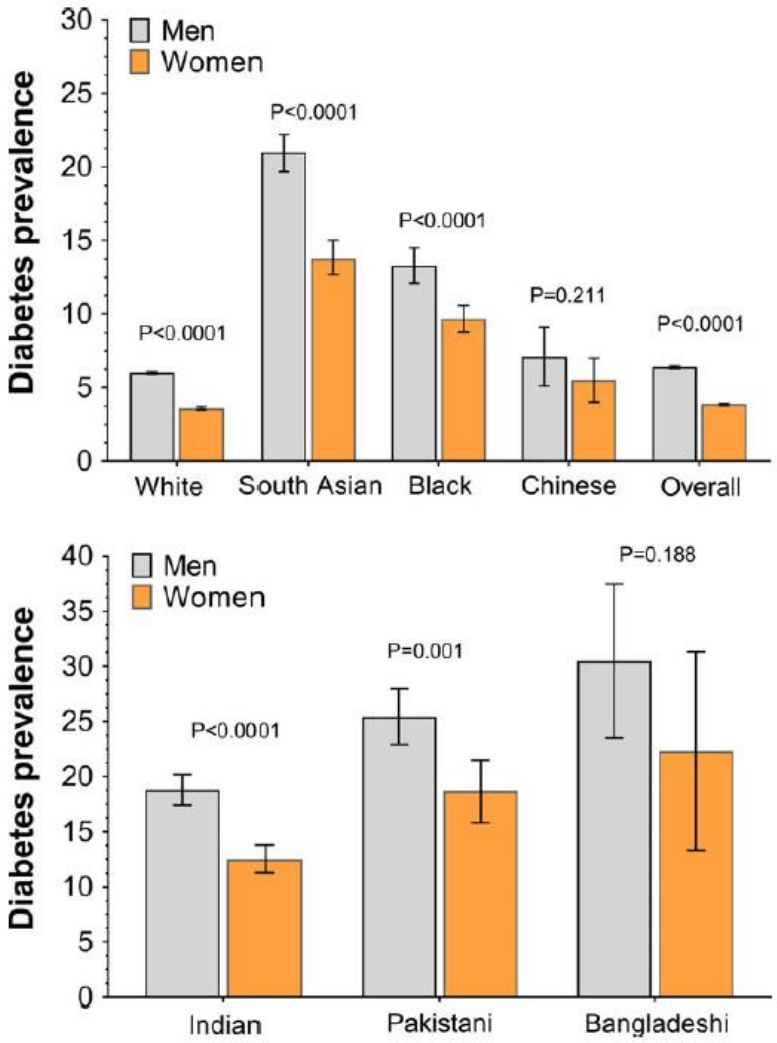
The risk of developing Type 2 diabetes increases as body mass index increases. Data from the 2018 Health Survey for England reports that the prevalence of total (diagnosed and undiagnosed) diabetes was 12% among obese adults (body mass index of 30kg/m^2 or greater) compared to 7% in those that are overweight (body mass index 25-29.9kg/m^2) and 5% in adults who were not overweight (body mass index less than 25kg/m^2) [10]. The distribution of body fat is associated with the risk of Type 2 diabetes with central obesity (measured by waist circumference) being associated with a greater prevalence. In the 2018 Health Survey for England 14% of men and 10% of women with a very high waist circumference (more than 102 cm and more than 88 cm respectively) had either diagnosed or undiagnosed diabetes. This compared to 6% of men and 3% of women with high waist circumferences (94-102cm and 80-88cm respectively) and 5% of men and 4% of women with a desirable waist circumference (less than 94cm and less than 80cm respectively) [10][1].

[1] Although these data relate to total diabetes prevalence (all types including Type 1 diabetes and others not associated with obesity the fact that, at a population level, the vast majority of adults with diabetes have Type 2 diabetes means that the associations shown here will be driven by the association between Type 2 diabetes and obesity as the number of people with other types will be very small.

Ethnic Variations in diabetes prevalence

Variation in the risk of Type 2 diabetes by ethnic group is well documented. In a recent analysis of the UK biobank [11] the ethnic differences in diabetes risk were easily apparent with multiple fold higher rates in South Asians, being highest in those of Bangladeshi origin, and lowest in those from India with risk being intermediate in those of Pakistani origin. Of further note, it was clear that Type 2 diabetes was more common in the male sex in each of these ethnicities than their female counterparts in age, body mass index and social class standardised analyses. There was also evidence for higher diabetes risk in those from Black ethnic groups but whether risk was greater in Chinese was less clear. These UK Biobank data are somewhat selected but even so, they allow good matching for usual confounders such as social class and body mass index and as a result they nicely demonstrate the variance in diabetes risks over and above such confounders.

Figure 1.3: (taken from Ferguson et al) Prevalence of diabetes mellitus by ethnicity and sex standardised for age, socioeconomic status, BMI, and lifestyle factors



The association between body mass index and risk of Type 2 diabetes varies by ethnicity. People from South Asian ethnic groups typically have a risk of Type 2 diabetes with a body mass index of 24 kg/m^2 that is equivalent to their peers from White ethnic groups with a body mass index of 30kg/m^2. Those from Black ethnic groups show a similar risk at a body mass index of approximately 27kg/m^2 [12].

Role of Social deprivation

There is a strong social deprivation gradient in the prevalence of Type 2 diabetes. 24.7% of the 1,681,331 people with Type 2 diabetes included in the 2012/12 National Diabetes Audit cohort lived in the most deprived fifth of areas compared to only 15.5% in the least deprived. The association between social

deprivation and established risk factors for Type 2 diabetes is not straight forward. People living in the more deprived areas are more likely to be from South Asian and black ethnic groups and are also more likely to be overweight or obese. On the other hand the age structure of areas with high levels of social deprivation is younger than among the more affluent areas. As a consequence it is not possible to attribute all the variation in prevalence of Type 2 diabetes to underlying social deprivation. However, the fact that psychological stress has been shown to be a factor in the onset of Type 2 diabetes [13] means that living in an area of high social deprivation and the associated stress means that an independent association cannot be ruled out.

Epidemiological considerations and future projections about prevalence

The fast onset of clinical symptoms in Type 1 diabetes means that it in epidemiological studies it is assumed that all those with the condition will be diagnosed. However, the more gradual nature of the development of Type 2 diabetes and the lack of life threatening symptoms mean that many people meet the criteria for the diagnosis of diabetes but are unaware of their condition. In 2008/09 it was estimated that 27% of people with diabetes had not yet been diagnosed [14]. Increasing awareness of the benefits of earlier diagnosis, and therefore management, of Type 2 diabetes amongst the clinical professions and the general public alongside specific public health interventions such as Health Checks for people aged 40 years and older has led to a reduction in the estimated proportion of people that are undiagnosed. In March 2019 3,319,266 people (6.9%) people aged 17 years and older included in general practice registers had a diagnosis of diabetes [8]. This compares to estimates based on trends in population characteristics (age and ethnic group structure) and obesity as measured by the Health Survey for England that 8.6% of adults aged 16 years and older meet the diagnostic criteria for diabetes. Demographic changes as the population structure ages and, in particular amongst those ethnic groups that have a higher prevalence of diabetes mean that by 2035 it is estimated that the total prevalence of diabetes among adults in England will increase to 9.7% [15].

Despite clear definitions of Type 1 and Type 2 diabetes and differing physiological causes the distinction between types of diabetes in clinical settings and epidemiological research is not always clearly and accurately recorded.

Different types of diabetes

There is also an increasing understanding and recognition of hybrid forms of diabetes (slow evolving immune mediated diabetes in adults and ketosis prone Type 2 diabetes) and other specific forms of diabetes including monogenic diabetes. Following changes to the definitions used to identify people with diabetes in the Quality and Outcomes Framework (a general practice quality based financial incentive scheme) a programme of work was undertaken to review the classification and coding of diabetes within clinical systems. As part of this a systematic review of existing literature was undertaken. It found that the misclassification of types of diabetes had potential consequences for treatment regimens and risk management of people with diabetes. Although studies included in the review were too heterogeneous to allow for results to be combined a common theme was that younger people were more likely to experience miscoding of type of diabetes [16]. An audit tool was developed to identify people with diagnosed diabetes where the type of diabetes may be misclassified based on other routinely recorded data. Testing and validation of this tool found significant levels of misclassification of types of diabetes recorded in clinical systems. In further analysis of 54,088 patients across nine general practices in Leicester 13.5% of people with a diagnosis of diabetes were identified as potentially being misclassified. After further examination of clinical records the percentage of those deemed to be misclassified fell to 7.4% [17]. This suggests that whilst there is a clear theoretical distinction between the types of diabetes the reality of clinical practice and routine data recording mean that data obtained from these sources may not always reflect the true underlying pathology. It also highlights the importance of cross validating data taken from routine clinical care with other variables recorded and undertaking appropriate sensitivity analyses around type of diabetes where the results are likely to be contingent on the grouping of diabetes types.

Complications of diabetes

Cardiovascular complications

People with diabetes are at greater risk of developing cardiovascular disease than those without hyperglycaemia. For those with Type 2 diabetes this risk is roughly double that in non-diabetes patients and begins to accumulate well before diabetes is diagnosed.

Heart failure occurs when the ability of the ventricles to fill or empty is reduced. It may follow damage to the muscle following an ischaemic event or be attributable to diabetic cardiomyopathy. Stroke is the term used to describe an event when the supply of blood is cut off. An ischemic stroke occurs when a cerebral blood vessel is obstructed whilst a haemorrhagic stroke is the result of a leak or bleed from a cerebral blood vessel. Other complications include peripheral vascular disease, linked to narrowing of the vessels that supply the legs.

Analysis from the National Diabetes Audit shows that in 2017/18 people with Type 1 diabetes were 3.8 times more likely to have a hospital admission for a myocardial infarction, 3.2 times more likely to have a stroke and 4.2 times more likely to be admitted to hospital for heart failure than their peers without diabetes. The comparable figures for people with Type 2 (and other types) diabetes were 2.0 for myocardial infarction, 1.8 for stroke and 2.4 for heart failure. Further analysis shows that the age is the strongest predictor of cardiovascular risk, followed by HbA1c and systolic blood pressure measured in the six years prior to the potential event [18].

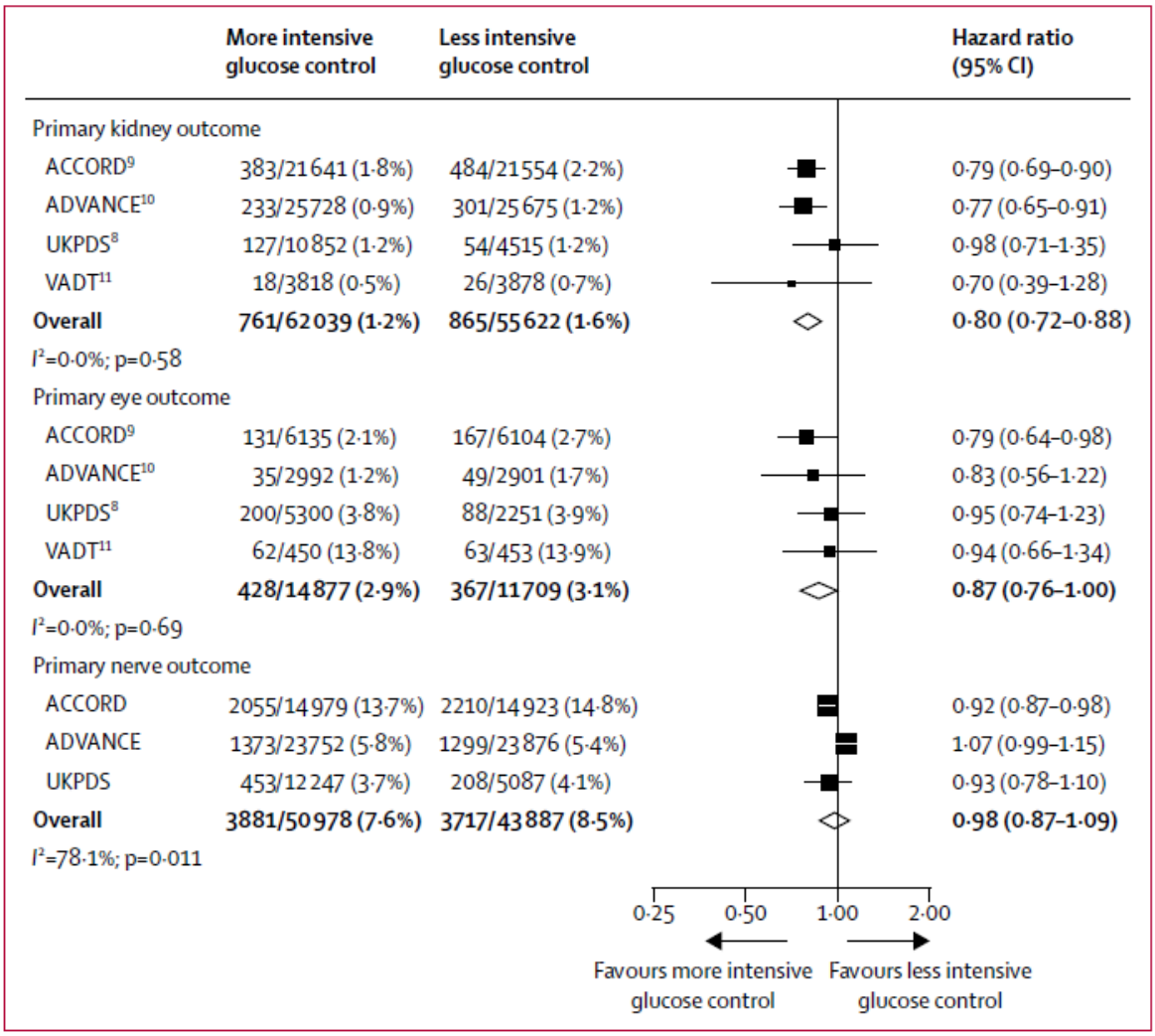
Microvascular complications

Hyperglycaemia increases the risk of microvascular disease. This may affect all body systems and blood flow is restricted by the narrowing of small blood vessels. Diabetic retinopathy occurs when the retina is damaged and micro aneurysms form. In more advanced disease new blood vessels are formed in the eye which may burst and cause bleeding which obstructs vision. In 2013, 5.4% of registrations for severe sight loss and 6.3% of sight impairment registrations in England and Wales were attributed to diabetic retinopathy and maculopathy

[19]. Kidney disease is a common microvascular complication of diabetes. As the glomeruli become damaged protein will leak from the blood into urine. Narrowing of the renal artery may also contribute to declining kidney function. The risk of end stage kidney disease (requiring dialysis or transplantation) is 17 fold higher for people with Type 1 diabetes and 3.6 greater for people with Type 2 diabetes compared to those without diabetes [18]. As the nervous system relies on the circulation system (and vice versa), the narrowing of small blood vessels can also lead to neuropathy. This may affect all areas of the body including peripheral limbs and the digestive system.

Risk for complications and effects of glucose reduction

Figure 1.4: Meta-analysis of effects of HbA1c reduction in microvascular outcomes in an individual participant meta-analysis of major landmark trials



Hyperglycaemia increases the risk of developing macro and microvascular disease. As a result people with diabetes are more likely than their peers to experience cardiovascular events, develop chronic kidney disease, sight loss due to retinopathy and maculopathy and have poor foot health leading to ulcers [20]. There is now strong evidence trial that reducing glucose levels per se lowers risks of the above complications although admittedly the findings for neuropathy from clinical trials is not as clear cut as one would imagine. In terms of cardiovascular disease (CVD), whilst results from several intensive glucose trials were somewhat disappointing for lowering of CVD risk, the pooling of such studies suggested around a 15% lower risk for coronary heart disease from around a 0.9% reduction in HbA1c levels. However, this meta-analysis also suggested no effect of such intensive glucose reduction on all-cause mortality [21], at least by treatment available at that time. Indeed, it should be remembered that such studies were done in an era before much of the newer drugs now proven to lower CVD were being used. More recently, a meta-analysis on microvascular events, showed intensive glucose reduction by around the same amount of 0.9% over a period of 5 years in major trials lowered kidney outcomes by 20%, and eye outcomes by 13% but no clear evidence for an effect on nerve outcomes (**Figure 1.4**, taken from Zoungas et al) [22].

Foot ulcers

People with diabetes have a much elevated risk of developing foot ulcers. There are a number of physiological factors that combine to create this elevated risk. Macrovascular damage to the main arteries in the lower body can reduce the flow of oxygenated blood to the lower leg and feet. This may be compounded by microvascular damage to blood vessels in the lower leg and foot. Neuropathy in the lower limb extremities can result in the loss of sensation (and neuropathic pain). This loss of sensation results in a greater risk of trauma and for the injury to go unnoticed for a substantial period of time. Diabetic foot ulcers are prone to infection which hinders healing. It is estimated that the prevalence of diabetic foot disease is 2-2.5% of those with diagnosed diabetes [23]. As a result of diabetic foot disease people with diabetes are approximately 23 times more likely to have a lower limb amputation than their peers without diabetes [24]. The medium to long term prognosis of people with diabetic foot disease is poor with only three fifths of people surviving for five years [23].

Mortality risks

Diabetes is associated with an increased risk of mortality. It is estimated that Type 1 diabetes results in a life expectancy reduction of 11 years for men and 13 years of life lost for women [25]. The loss of life expectancy associated with a diagnosis of Type 2 diabetes varies by age, sex and social deprivation with greater losses amongst younger adults, those living in deprived areas and females [26]. In 2017 there were 6040 deaths where the primary cause of death was diabetes in England and Wales [27] but comparisons of mortality rates for the same year in people included in the National Diabetes Audit suggest 32,000 more deaths than would be expected based on mortality patterns amongst their peers [28]. This indicates that the vast majority of additional mortality risk experienced by people with diabetes is attributable to the greater risk of cardiovascular, microvascular and other complications rather than severe hypo and hyperglycaemic events.

The evidence for improving diabetes related outcomes

The Randomised Controlled Trials Diabetes Control and Complications in people with Type 1 diabetes (DCCT) [29] and UK Prospective Diabetes Study in Type 2 diabetes (UKPDS) [30] established that hyperglycaemia and, for type 2, raised blood pressure are pathogenic factors for diabetic retinopathy. The long-term observational follow-up studies of their cohorts EDIC for DCCT [31] and UKPDS 10yr for UKPDS [32] also generated evidence that hyperglycaemia and raised blood pressure might influence the incidence of further microvascular and cardiovascular complications. These epidemiological follow-up observations following closure of the randomised controlled provided some evidence of a 'legacy effect' of metformin on cardiovascular disease whereby the patients in the original metformin intervention group had fewer cardiovascular events and deaths despite post trial convergence of glucose levels. Another randomised trial (VADT) in Type 2 diabetes [33] found that lower glucose levels (6.9% vs 8.4%) were associated with fewer cardiovascular events only when there was clear separation of HbA1c between the control and intervention groups. In VADT there was no effect on mortality but in the ACCORD Type 2 diabetes study [34] the intervention group in which an HbA1c of below 42mmol/mol was targeted, myocardial infarction events reduced but mortality increased. Overall, from the intensive glucose lowering trials, there was evidence for a benefit on non-fatal

cardiovascular disease but no improvement in total mortality. Accordingly, concerns persist about the strength of the evidence, particularly in respect of severe disabling or life-threatening long-term outcomes for optimal glucose levels in both Type 1 [35] and Type 2 diabetes [36]. Also, many studies have excluded heart failure which is emerging as one of the most prevalent and harmful cardiovascular complication of diabetes [37]. Furthermore, debate is ongoing about whether the hazards of glucose lowering treatment outweighs its benefits when levels are lowered closer to normal using conventional treatments [36] and about the use of surrogate markers of treatment efficacy, such as HbA1c [38].

Classes of drugs shown to lower outcomes

More recently, two newer classes of drugs used in diabetes have been shown to lower cardiovascular and related outcomes. These are important results since established classes of drugs have either relatively modest evidence for such benefits (i.e. metformin) or lack such trial evidence (sulphonylureas) or have neutral effects (DPP-4 inhibitor classes). These two newer classes include the sodium-glucose cotransporter-2 inhibitor (SGLT2i) and the Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RA) classes. The former SGLT2i class works by enhancing the urinary excretion of glucose at lower glucose levels, whereas the latter class work as incretin hormones to enhance insulin release, though they also help aid weight loss. As shown in a recent meta-analysis [39] (**Figures 1.5a-d**), class lower hard renal outcomes most strongly, followed by heart failure, with a lesser reduction in major adverse cardiovascular outcomes (MACE), driven mostly by a reduction in CVD death. The benefits on MACE seem to be restricted to those with existing ASCVD whereas other benefits were evident in all groups of patients recruited into the trials. The benefits seem to occur independently of baseline HbA1c levels and of any changes in HbA1c. The current best thinking is that this class of drugs leads to haemodynamic benefits that lessen nephron/ glomerular stress (and so sizeable reductions in renal outcomes) and lead to reduced cardiac workload by reducing both cardiac pre- and afterload, and so are associated with less heart failure and subsequently fewer less cardiovascular deaths. However, many other potential mechanisms remain possible and this is the subject of considerable ongoing work.

Figure 1.5a. Risk of MACE by SGLTi trials by baseline ASCVD or multiple risk factors

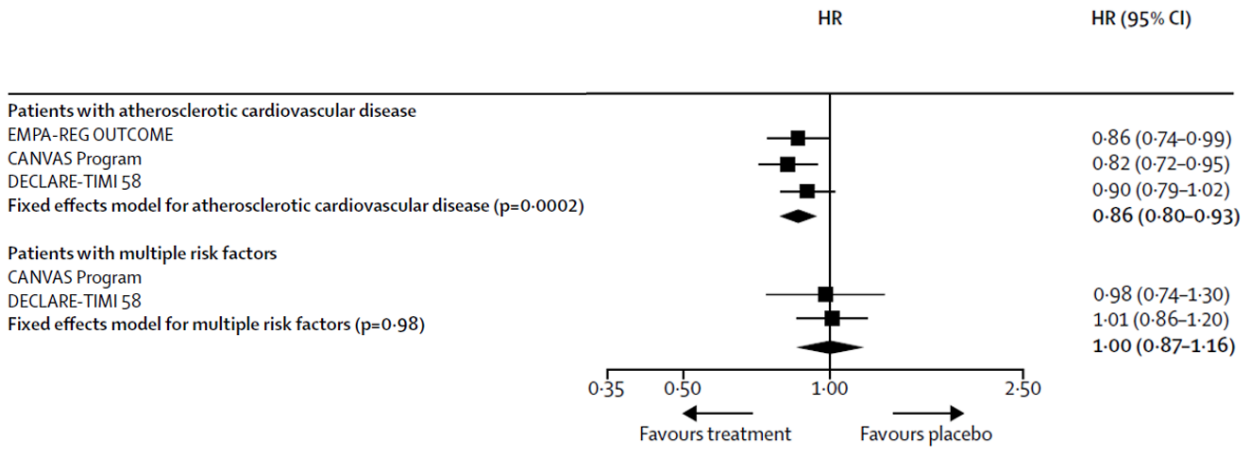


Figure 1.5b Heart hospitalisation and CVD death by Meta-analysis of SGLTi trials by baseline ASCVD or multiple risk factors

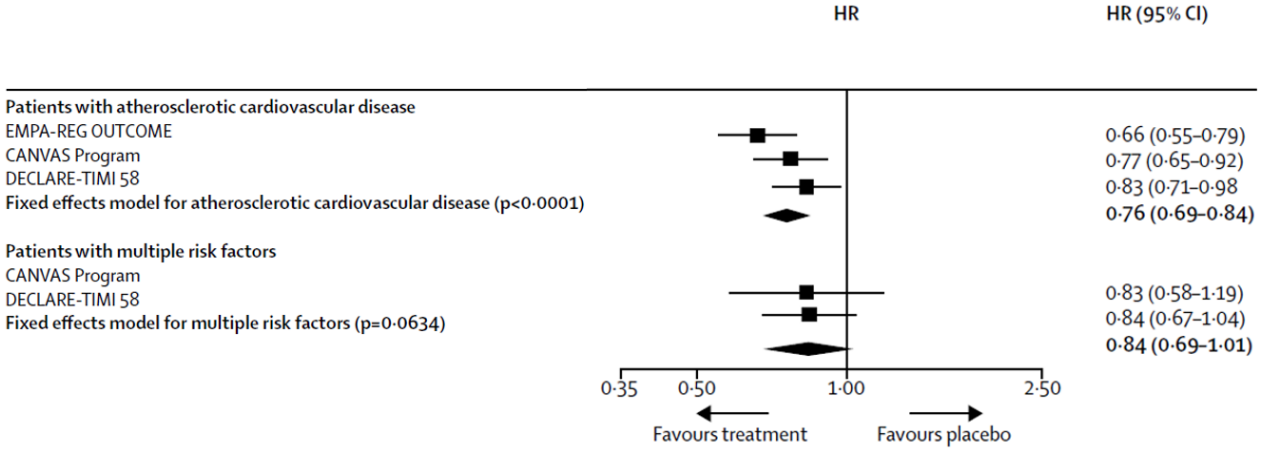


Figure 1.5c Heart hospitalisation and CVD death by Meta-analysis of SGLTi trials by baseline history of heart failure

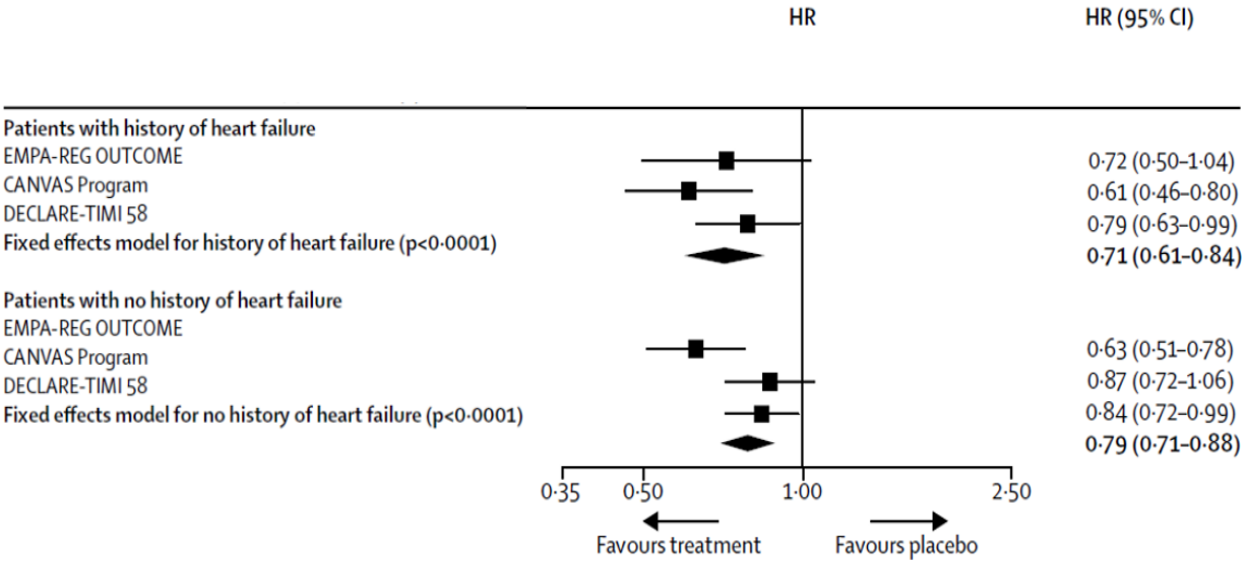
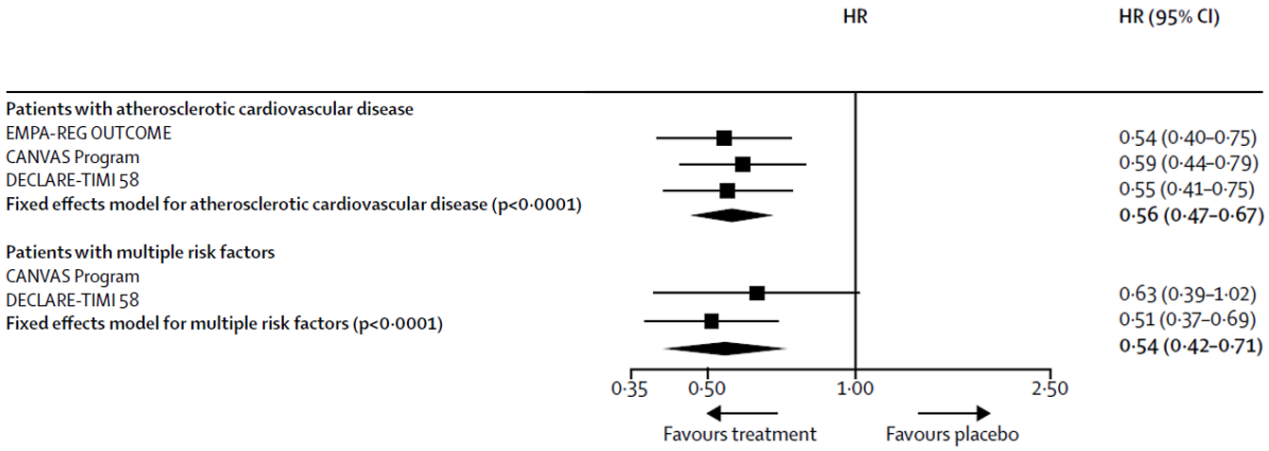


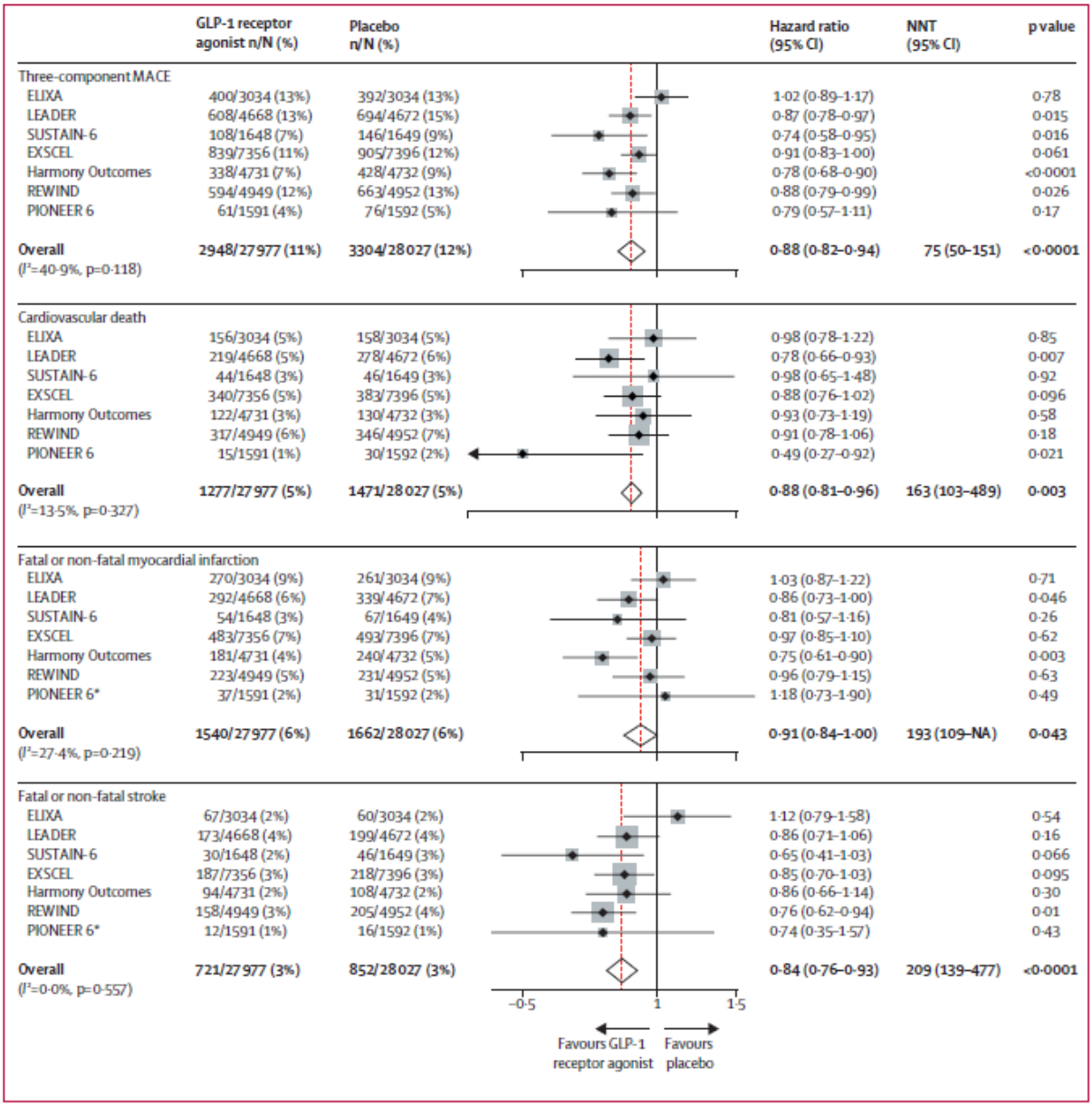
Figure 1.5d Risk for renal outcomes in SGLTi trials by baseline ASCVD or multiple risk factors



Figures 1.5a-d from Zelniker et al. Meta-analysis of different outcomes (MACE, Heart failure/ CVD death or renal disease) from SGLTi trials by baseline characteristics.

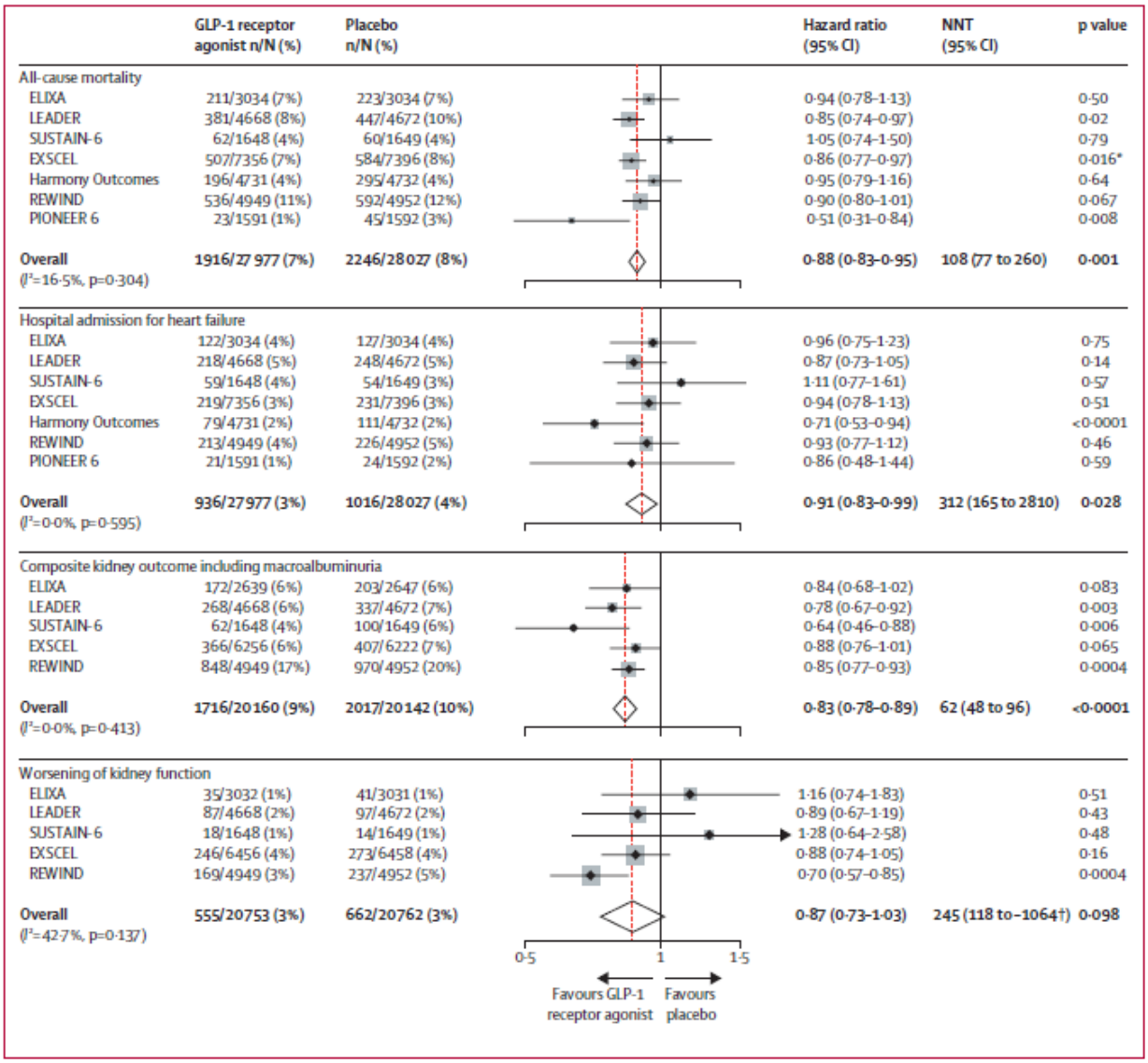
For GLP-1RA, a separate meta-analysis [40] (**Figures 1.6a-b** from Kristensen et al, see below) showed these agents also lower MACE, CVD death, total mortality as well as a hint to lowering incident heart failure. The benefits on hard renal outcomes seemed more variable. Furthermore, benefits on MACE seemed to extend beyond those with prior ASCVD to those with evidence of disease but no prior MI or stroke. The benefits of GLP-1RA, like those of SGLT2i, also seemed to occur independently of baseline HbA1c.

Figure 1.6a Risk of MACE and each of its components. Figure from Kristensen et al



Three-component MACE consisted of cardiovascular death, myocardial infarction, and stroke. NNTs are calculated over an estimated median follow-up of 3·2 years. MACE=major adverse cardiovascular events. GLP-1=glucagon-like peptide-1. NNT=number needed to treat. *For PIONEER 6, data for fatal and non-fatal myocardial infarction and stroke were not available, so numbers and estimates refer to non-fatal myocardial infarction and non-fatal stroke exclusively.

Figure 1.6b: All-cause mortality, hospital admission for heart failure, and kidney outcomes. Figure from Kristensen et al.



The consequence of the results of these outcome trials is that new guidelines for the use of these agents have been published by Diabetes- and cardiology-led guidelines, as recently published [4,41]. Both have now accepted that these two classes of drugs can be used independently of baseline glycaemia. There remains ongoing debate whether baseline metformin is necessary in treatment naïve patients who are recommended for these therapies, as well as what class of drug should be recommended and in what circumstance. Equally, there is uncertainty and debate on the use of these drugs to patients without existing cardiovascular disease, renal disease or heart failure.

The current clinical management of people with diabetes is based around guidance issued by NICE [42,43]. It focuses on identifying and reducing the risk of developing diabetic complications by reducing hyperglycaemia and minimising established cardiovascular risk factors through lifestyle and pharmaceutical interventions. There is now clear evidence for substantial benefits of lipid-lowering and blood pressure management in the care of people with diabetes [21]. With regards to blood pressure, many patients with diabetes have hypertension, and the Angiotensin converting enzyme (ACE) inhibitors and Angiotensin receptor blockers (ARB) classes of drugs have been shown to have specific benefits in lessening proteinuria or its progression. Blood pressure targets have also been tightened over the decades so that control of blood pressure has improved in many countries in people with diabetes. Certainly, most people with diabetes should have systolic blood pressure levels targeted to below 140 mmHg and arguably, many younger patients should seek levels below 130 mmHg. With respect to cholesterol, these targets have also been reduced over the years and many patients with Type 2 diabetes are now on statins. Indeed, it appears as if CVD risk reduction is more greatly reduced by blood pressure and lipid lowering than it is by glucose reduction per se, at least over the course of 5 years. By contrast, the evidence base for aspirin in primary prevention in diabetes and in general has weakened, though it remains critical in secondary prevention. Hence, NICE recommendations correctly focus on comprehensive risk factor management to prevent future complications.

Database Research in Diabetes: Real World Evidence

Over the last ten years there has been an expansion in the use of large datasets based information routinely recorded in the course of clinical care to explore the epidemiology of diabetes. This has predominately been made possible by the use of electronic systems to record clinical information at the point of care delivery [44].

The data included in real world datasets is recorded as part of clinical practice. This has both positive and negative implications. Firstly, it provides the ability to access large scale data without the considerable time and costs associated with specific research data collections. It also is less likely to have significant sample bias. The populations recruited to randomised control trials are rarely

representative of the full patient population for which they seek to provide evidence for clinical practice [44,45]. By collating data from the full range of people under the care of a clinical service the data represents the greater variation in patient characteristics, especially those with multi-morbidity and other more complex needs. On a less positive note the completeness and quality of the data may not be as high as would be expected within a similar cohort where data was primarily collected for research purposes. The definitions used will be defined by the primary use of the data which may include performance monitoring and financial arrangements and may be subject to change over time. The data collected will also be subject to potential differences in clinical behaviour between individual clinicians and organisations.

The National Diabetes Audit in England and Wales

The National Diabetes Audit (NDA) was established in 2003 to assess the quality of, and variation in, diabetes clinical care and outcomes in order to inform service improvement across England and Wales. It addresses five specific questions

- Is everyone with diabetes diagnosed and recorded on a practice diabetes register?
- What percentage of people registered with diabetes received the nine National Institute of Health and Care Excellence (NICE) key processes of diabetes care?
- What percentage of people register with diabetes achieved NICE defined treatment targets for glucose control, blood pressure and blood cholesterol?
- What percentage of people registered with diabetes are offered and attend a structured education course?
- For people with registered diabetes what are the rates of acute and long term complications (disease outcomes)?

The NDA is managed by NHS Digital in partnership with Diabetes UK. It is one of more than 30 National Clinical Audits commissioned by the Healthcare Quality Improvement Partnership on behalf of NHS England and the Welsh Government. In England the legal basis for the NDA collection and use is (since 2017) provided by a 'direction' under section 254 of the 2012 Health and Social Care Act from

NHS England to NHS Digital; in Wales it is granted section 251 approval by CAG (which applied in England up to 2016). The NDA has, under these regulations the information governance permissions for access to the dataset to answer specific research questions.

The National Diabetes Audit collates data on every person registered at participating health providers with a coded electronic record of diagnosed diabetes mellitus. From 2017/18 people with Non-Diabetic Hyperglycaemia have been added. Women with gestational diabetes are not included. Participation in the audit is open to all primary and specialist care healthcare providers in England and Wales with data extracted from electronic patient records. Between 2003/04 and 2016/17 participation for primary care was through an opt in process. Some electronic clinical systems provided the facility to automatically create and submit the required data extract. From 2017/18 onwards participation in the audit was automatically undertaken by primary care electronic clinical systems with the option to opt out of data collection process either as a general practice or as an individual with diabetes. Participation of specialist secondary care health service providers is by submission of an extract from their electronic clinical system. The data collation process is managed and undertaken by NHS Digital which is the national provider of data and IT systems for the NHS.

Between the audit years 2003/04 and 2018/19 a total of 4,714,395 people were included in at least one NDA data collection. Between 1st January 2005 and 31st December 2018 there were 1,028,560 deaths recorded among people who were recorded in one or more audit data collection round. Further demographic details of the people included in the cohort are listed in **Table 1.1**.

There is an annual data collection for the NDA. Each data collection extracts data for a 15 month period running from the beginning of January in the first year to the end of March the next year. For example, the data collection for 2017/18 collects data recorded between 1st January 2017 and 31st March 2018. Until 2016-17 only the latest recorded data and measurements in each audit period were included in the dataset but since then all values have been extracted e.g. all instances of HbA1c or blood pressure measurement.

Demographic data (date of birth, sex, date of diabetes diagnosis, ethnic group) from across data collection periods has been combined to minimise missing data and ascertain the most likely true value for each individual. Where an individual has been included in the NDA in multiple years and there is variation in the demographic data provided for different time periods the most commonly reported value is taken to be the most likely to be accurate. If no single value has been provided more frequently, the latest value is taken to be the most accurate.

Table 1.1: Characteristics of people included one or more data collection of the NDA, 2003/04 to 2018/19

		Type 1 diabetes	Type 2 diabetes	Other types of diabetes	Type of diabetes not stated
Sex					
	Male	204,292	2,307,554	31,025	45,659
	Female	157,040	1,852,282	38,417	70,216
	Not stated	15	57	12	7,826
Year of birth					
	Pre 1930	15,410	487,067	5,425	29,891
	1930-1939	29,148	891,576	7,551	18,774
	1940-1949	39,267	1,031,893	10,263	14,077
	1950-1959	47,883	852,641	10,764	10,631
	1960-1969	60,713	583,137	10,929	10,247
	1970-1979	51,549	237,367	11,319	12,655
	1980-1989	48,421	64,148	9,017	12,866
	1990-1999	42,465	10,523	3,063	3,735
	2000 onwards	26,461	1,167	1,019	611
	Not stated	30	374	104	10,214
Year of diagnosis					
	Pre 1970	17,691	8,215	137	755
	1970-1979	26,728	16,808	193	961
	1980-1989	44,892	91,025	485	3,296
	1990-1999	84,822	500,418	1,949	13,539
	2000-2009	111,930	1,815,958	10,499	26,749
	2010 onwards	71,287	1,700,626	48,455	8,338
	Not stated	3,997	26,843	7,736	70,063
Ethnic group					
	White	267,386	2,645,756	39,843	50,942
	Mixed	4,084	37,837	750	864
	Asian	18,688	443,174	7,254	6,152
	Black	12,472	169,337	2,716	3,204
	Other	6,724	86,356	1,593	1,987
	Not stated	51,993	777,433	17,298	60,552

Table 1.1 sets out the categories of data collected for each audit period of the NDA. Demographic data is collected for each individual included in the audit for each time period. This provides date of birth, sex, date of diabetes diagnosis, type of diabetes, ethnic group and lower super output area of home address (to identify geographical location and allocate social deprivation score). The care process data comprises the date and result of HbA1c, blood pressure, total serum cholesterol, urinary albumin/creatinine ratio, serum creatinine, body mass index measurements, smoking status and foot examination. Eye screening data is held in the screening programme management systems that have hitherto been unable to link to the other core data; it is hoped that this will become possible for 2019/20 data.

The use of insulin pumps and the reasons for starting to use them is provided by a specific data collection undertaken by specialist healthcare providers for those under their care. The co-morbidities of learning difficulties and severe mental illness are identified through the recording of a diagnosis in the general practice record. From 2017/18 onwards the NDA has collected data on all prescriptions issued for glucose lowering agents, anti-hypertensive drugs and statins.

Table 1.2: Data collected for each audit period

	2003/04	2004/05	2005/06	2006/07	2007/08	2008/09	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15	2015/16	2016/17	2017/18	2018/19
Demographic data	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Care processes	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Hospital admissions	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Co-morbidity of learning difficulties													✓	✓	✓	✓
Co-morbidity of severe mental illness													✓	✓	✓	✓
Use of insulin pump including reason for use of device													✓	✓	✓	✓
Glucose lowering drugs, statins and anti-hypertensive drugs															✓	✓
Date and cause of death	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

The NDA has an established links to the Hospital Episode Statistics (HES) for England and Patient Episode Database for Wales (PEDW) to identify all hospital admissions that occur in people included in one or more audit collection process. The cohort is also linked to death registrations compiled for England and Wales by the Office for National Statistics. This provides the date and cause of death for all people who have been included in one or more NDA data collection. Monitoring of year on year recording of care processes and intermediate clinical outcomes (HbA1c, blood pressure and total cholesterol) has shown that between 2003/04 and 2006/07 there was a significant rise in the proportion of people meeting the then recommended target of a HbA1c of 58mmol/mol or less from 56.3% to 62.6%. However, this proportion had only increased marginally to 63.3% in 2010/11 and 65.0% in 2017/18. Similar patterns were shown in the proportion of people achieving the recommended targets for blood pressure and cholesterol. This suggests that whilst there were documented substantial improvements in the attainment of recommended treatment targets in the early years of the NDA this improvement appears to have reached a plateau [46].

Data from the 2012/13 NDA cohort was used to identify how the current 'real world' outcomes of people with newly diagnosed Type 1 diabetes compare with the landmark Epidemiology of Diabetes Interventions and Complications (EDIC) study intervention and control groups. This found that a broadly similar cohort from the NDA in 2012/13 had a mean HbA1c of 72mmol/mol compared to 56mmol/mol and 76 mmol/mol in the intensive treatment and control arms of the EDIC study. A cohort of people with Type 2 diabetes matching the criteria for the UK Prospective Diabetes Study (UKPDS) was also identified. This group had a mean HbA1c of 57 mmol/mol compared to 53 mmol/mol in the intensive treatment and 63 mmol/mol in the conventional treatment arms of the UKPDS. These comparisons provide an insight into how real world clinical outcomes compare to key trials and highlight that whilst considerable improvements have been seen in the intermediate clinical outcomes for those with Type 2 diabetes further progress is required to improve outcomes and close the gap between what can be shown in research settings and real world outcomes in people with Type 1 diabetes [47].

Variations in outcomes by ethnic group have been documented using data from the NDA. After adjusting for demographic characteristics (age, sex, social deprivation), type and duration of diabetes, cardiovascular risk factors (HbA1v, blood pressure, cholesterol, body mass index) and hospital admissions people from South Asian and Black ethnic groups had lower short term mortality than those from white ethnic groups (Odds ratio 0.533 95% CI 0.504-0.563 and 0.529 95% CI 0.487-0.574 respectively) [48].

Each year a report detailing the demographic characteristics and intermediate clinical outcomes of people with diabetes are produced by the NDA team. Further reports are produced which examine hospital admissions for cardiovascular and other diabetes related complications and mortality. A full list of the NDA reports can be found at https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-audit.

The strength of this cohort is that it is representative of the vast majority of people with diabetes and in 2017/18 included over 95% of the people registered with diagnosed diabetes across England and Wales. The significant size of the cohort means that it is possible to identify statistically significant variation amongst sub-groups that make up a small proportion of the population with diabetes, for example, those from minority ethnic groups and those diagnosed with Type 2 diabetes in early adulthood.

The primary weakness of the data is that it is drawn from information recorded as part of routine clinical care rather than specific data collected for research purposes. This means that there may be more variation in the interpretation and use of clinical codes than would be found amongst data obtained through a specific data collection process. The rate of missing data is also likely to be higher. The fact that the data collated for each audit period used until 2017 only the latest recorded measurement in the period means that in the past some detail of the variation in clinical measures has not captured. The breadth of the data collected is more limited than many research cohorts but recent additions, such as the inclusion of drug data and identification of learning difficulties and severe mental illness, mean that the cohort will have the scope to address broader questions in the future.

Other data sets

There are of course other national datasets. Most notable for their contribution to contemporary diabetes epidemiology are those from Scotland, Sweden and Denmark as well work from USA. There are also notable papers from other sources. Recent reviews have collated mortality and other statistics from multiple national cohorts, with a notable recent review paper [49] showing declines in mortality in diabetes over time but other secular changes by age of patients with diabetes (**Figures 1.7a to 1.7b**).

Figure 1.7a: Trends in rates of all-cause mortality among populations with diagnosed type 2 diabetes. Taken from Gregg et al

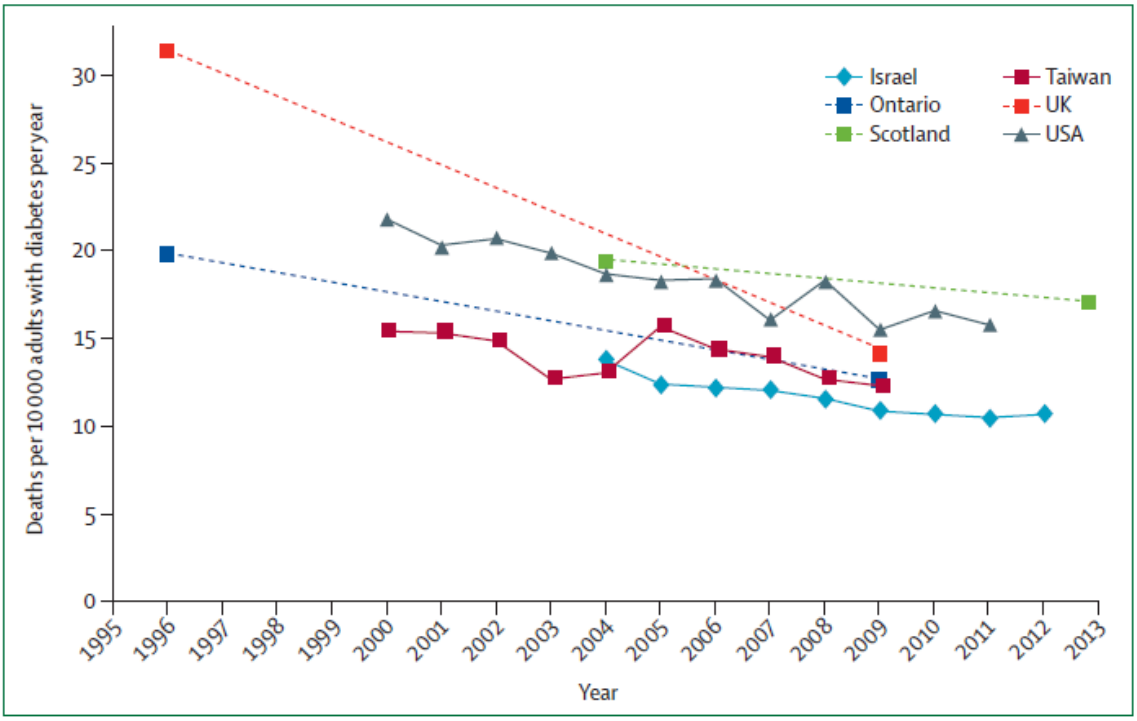
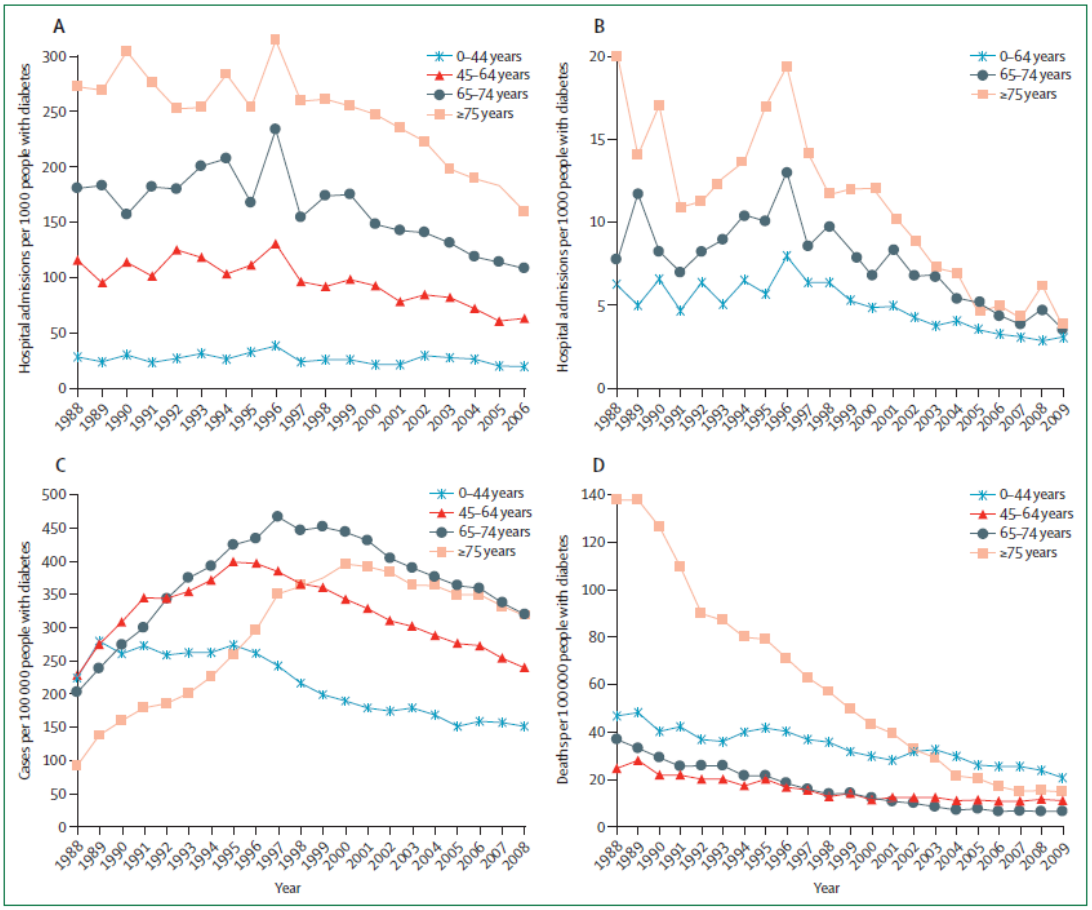


Figure 1.7b: Trends in major diabetes complications by age among people with diagnosed diabetes in the USA. Taken from Gregg et al



As current demographic and lifestyle trends mean that the prevalence of diabetes is likely to rise with an estimated 4.8 million people (9.5% of the population) having diabetes (either diagnosed or undiagnosed) by 2030 [14,50]. It is estimated that 10% of National Health Service expenditure can be attributed to diabetes and its complications and this proportion will rise to 17% by 2035 [51]. Understanding the characteristics and outcomes of people with diabetes is vital to improving clinical care and reducing morbidity and mortality. Using routinely collected data offers an efficient way to scrutinise data on large cohorts of people in a 'real world' setting.

Chapter 2: Context and Methods

Context of the range of work undertaken in this PhD

The work detailed in this thesis represents a long journey that was not always linear and was shaped by changing NHS structures, national developments in data governance and shifting perceptions around the use of large datasets. In 2006 I was fortunate to start work at the Yorkshire and Humber Public Health Observatory on their emerging national programme of work on diabetes. The Yorkshire and Humber Public Health Observatory was jointly hosted by the then Yorkshire and Humber Strategic Health Authority and the University of York. This organisational position meant that I had access to NHS based databases and was working in an environment that encouraged innovative approaches to data analysis and presentation. During this time, I expanded my technical knowledge and developed an understanding of diabetes through close working relationships with clinical colleagues. The 2012 Health and Social Care Act resulted in a fundamental reorganisation of the NHS England. As part of this in April 2013 the work of Public Health Observatories was subsumed into the newly established civil service organisation, Public Health England.

After realising that research was where my heart was and that the shift of the Public Health Observatories into Public Health England would change the focus of my employed work and offer fewer opportunities to innovate and explore data I registered for a PhD under the supervision of Professor Naveed Sattar in 2013. As well as providing a more formal basis for my research endeavours this offered the opportunity to undertake interesting projects that would not have reached the required priority to become part of the formal work programme of Public Health England. The original plan was to utilise the National Diabetes Audit to explore variation in outcomes in people with diabetes by ethnic group. Formal data access requests were lodged within a couple of months of registration. However, this coincided with a sudden and fundamental change in the interpretation and application of the information governance rules for large scale health datasets. The fact that patient level data on hospital admissions had been made available to private companies for commercial analysis became public knowledge. At a similar time public and professional support for the large scale care data programme to expand centralised data collection of routine clinical records to all activity within general practice was withdrawn

(https://www.bbc.co.uk/news/health-26259101). This led to the Inquiry into the Handling of NHS Patient Data by the Health and Social Care Select Committee in 2014 (https://www.parliament.uk/business/committees/committees-a-z/commons-select/health-committee/inquiries/parliament-2010/handling-nhs-patient-data/). These events led to a very cautious culture around sharing patient level data across NHS data analysis organisations and an effective ban on establishing new data sharing arrangements. As a result, no agreement around access to the NDA data could be reached until August 2017. The work presented in Chapters 6, 7 and 8 was undertaken whilst on an honorary contract with NHS Digital between September and December 2017.

The National Diabetes Audit for England and Wales

The National Diabetes Audit (NDA) for England and Wales was established in 2003 to assess the quality of, and variation in, diabetes clinical care and outcomes in order to inform service improvement across England and Wales. It addresses five specific questions

- Is everyone with diabetes diagnosed and recorded on a practice diabetes register?
- What percentage of people registered with diabetes received the nine National Institute of Health and Care Excellence (NICE) key processes of diabetes care?

  What percentage of people register with diabetes achieved NICE defined treatment targets for glucose control, blood pressure and total blood cholesterol?
- What percentage of people registered with diabetes are offered and attend a structured education course?
- For people with registered diabetes what are the rates of acute and long-term complications (disease outcomes)?

Every patient with a diagnosis of diabetes (except gestational diabetes) is eligible to be included in the NDA. Data on patient demographic characteristics, the care processes received and the results of care processes that are routinely recorded in clinical systems are extracted and compiled. The first data collection covered the time period 1st January 2003 to 31st March 2004 and

included 250,400 people with diagnosed diabetes registered with 3,886 general practices. The 2017/18 data collection included information on 3,398,469 people from 7,435 general practices and 114 specialist healthcare providers. Since its inception the NDA has linked the information provided by primary care and specialist healthcare providers to routinely compiled data sources on hospital admissions (Hospital Episode Statistics for England and Patient Episode Database for Wales). Analysis has identified the occurrences of hospital admission for cardiovascular disease (myocardial infarction, heart failure, stroke and angina), end stage kidney failure, lower limb amputation and diabetic ketoacidosis. From 2010/11 data linkages have also been made to death registrations compiled by the Office for National Statistics (see below for further detail). In 2015/16 data collected by the NDA was extended to include an indication of individuals who had a comorbid diagnosis of severe mental illness or learning disabilities. Specialist healthcare providers were also invited to provide the details of people using an insulin pump.

One of the significant limitations of the NDA has been the lack of data on drugs prescribed to individuals with diabetes. From 2017/18 onwards the scope of the audit has expanded to include prescription data for glucose lowering drugs, anti-hypertensive medications and statins. Whilst the primary purpose of this data is no assess the extent to which people with diabetes are receiving the care set out in NICE guidelines, the inclusion of this information significantly extends the scope and nature of the research questions that the NDA can address. It also gives scope to validate the information provide on types of diabetes.

Over the 16 years that the NDA has been in operation there have been a number of developments to the data collation mechanisms and the information governance structure for processing the data. There have been advances in the automation of data collection from electronic clinical systems initially through establishing bulk data extractions with system suppliers and latterly by using the General Practice Extrication Service (https://digital.nhs.uk/services/general-practice-extraction-service) which has facilitated the wider participation in the audit and increasing coverage of people with diabetes.

The analysis of the NDA data presented in Chapters 6, 7 and 8 is limited to patients receiving care from a healthcare provider in England. At the time of undertaking this work, the legal basis for holding the patient level data of individuals under the care of Welsh healthcare providers was uncertain.
The details above refer to the Core NDA, which now provides an annually updated dataset. It was recognised that it provided a wealth of information but that its full potential was not being realised and that there were many aspects of diabetes care and outcomes that were not covered by the existing methodology and dataset. In 2008, NHS Diabetes undertook a large scale national consultation with the diabetes community to identify areas to develop the NDA. The resulting programme of work included establishing and piloting a national diabetes inpatient audit, an audit of pregnancy in women with diabetes and an audit of care and outcomes for people with diabetic foot disease. Steering groups were established to identify the audit questions, define a dataset to answer the questions, design and test a data collection and analysis plan.

The NDA is managed by NHS Digital in collaboration with Diabetes UK under contract from NHS England and the Welsh Assembly. It is part of the National Clinical Audit and Patient Outcomes Programme that is commissioned by the Healthcare Quality Improvement Partnership.

Hospital Episode Statistics

Since 1989 the NHS has been compiling data on hospital activity including inpatient and outpatient care in the form of Hospital Episode Statistics (HES) (https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/hospital-episode-statistics). The primary purpose of this data is to inform payments to healthcare providers but it is also a valuable data resource for public health analysis and research. Access to HES was via pre-existing organisational data sharing agreements between Yorkshire and Humber Public Health Observatory/Public Health England and NHS Digital (including predecessor organisations). This facilitated access to the full set of variables within the patient level dataset subject to rules on the presentation of small numbers to protect individual confidentiality.

Chapter 3 is an analysis of HES to investigate inpatient mortality among people with diagnosed diabetes. A strength of this work is the factor that it was able to include every NHS hospital admission in England over a two-year period. This census (rather than sample) approach ensures the data analysis is representative and results are obtained with a high degree of statistical significance. However, the use of HES data as a stand-alone dataset has some limitations. Other measures of hospital mortality compiled by NHS Digital and its predecessor organisations link HES data to death registrations to identify any deaths within a specified period of discharge from hospital (https://digital.nhs.uk/data-and-information/publications/ci-hub/summary-hospital-level-mortality-indicator-shmi, Strengths and weaknesses of hospital standardised mortality ratios, BMJ 2011; 342 https://doi.org/10.1136/bmj.c7116). This provides a more patient centred and holistic view of hospital outcomes. The analysis presented in Chapter 3 would have been greatly improved by taking a similar approach. Unfortunately, the prevailing information governance climate at the time (see above) meant that it was not possible to obtain the necessary approvals to establish a new data linkage. Another potential imitation of using HES to consider outcomes for people with diabetes is the reliance on discharge coding to identify the clinical reason for the hospital stay and any contributing co-morbidities. At the end of each episode of hospital care (a period of care provided by a single hospital consultant) clinical teams produce a discharge summary. This, alongside other clinical notes if required, is used by teams of clinical coders to allocate ICD-10 codes for the primary and up to 12 secondary diagnoses for the hospital stay. An analysis of a specific cohort of the NDA (i.e. people known to have diagnosed diabetes) linked to HES data showed that in 2007/08 a significant proportion of people with diabetes did not have the condition identified as a co-morbidity in discharge coding for their hospital stay [52]. However, those people with diagnosed diabetes who did not have a diagnosis of diabetes recorded within the record for their hospital admission had similar lengths of stay and re-admissions rates rather than the substantially elevated use of hospital services shown amongst those with diabetes included in their discharge coded conditions. This suggests that whilst the coding of diabetes as a co-morbidity in HES was not complete at this time it was reasonably accurately identifying those in whom co-morbid diabetes was having a detrimental effect on their inpatient stay.

Death registrations

The Office for National Statistics compiles a database of all deaths registered in England and Wales. This includes demographic characteristics of the deceased and the date, location of death and cause of death. Cause of death is classified using the International Classification of Diseases version 10 (ICD-10) (https://www.who.int/classifications/icd/icdonlineversions/en/). The information provided on the death certificate by the doctor certifying death is categorised using an automated coding system, which gives one underlying cause of death and up to nine secondary causes (https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/methodologies/userguidetomortalitystatisticsjuly2017). As is common practice, all analyses presented in this thesis are based on the underlying cause of death.

Statistical methods

The subsequent chapters of this thesis report the results of a number of statistical analyses and use a variety of statistical tests and models.

In order to test an association between two categorical variables Pearson's chi-squared test (often referred to simply as chi-squared test) is used. This is a commonly used test to identify is there is a statistically significant difference between the observed and expected frequencies of two variables using a contingency table. The calculation identified the expected number of cases that would occur in each combination of variables if they were evenly distributed across the categories (the null hypothesis). These values are compared to the actual distribution of variables and the resulting values are compared to the chi-squared distribution to identify statistical significance.

The statistical difference between two continuous variables can be assessed using the Student's t-test. This test assumes that the two variables being compared follow a continuous distribution with a known mean. Different calculations are used depending on whether the variation of the two variables is considered to be the same or not. Where the relationship between a categorical variable with more than two categories and a continuous variable is considered a

group of calculations called Analysis of Variance or ANOVA are used. They are an extension of the t-test.

The two statistical tests listed above facilitate the comparison of two variables to identify statistically significant associations and differences. However, epidemiological analyses often require an understanding of how multiple potential explanatory variables are associated with a specific outcome. This requires statistical models that calculate multiple associations at the same time to be used. Logistic regression is a statistical model that estimates the probability of a binary event occurring. Categorical and continuous variables can be used to explain variation in the probability of the event occurring. A logistic regression model calculates the logarithm of the odds of the specific event occurring for each category of any categorical variables included in the model. The logarithm of the odds associated with a change of a single unit in a continuous variable is also computed. These values can be used to provide the odds ratio (and associated confidence intervals) for each value within a categorical variable and a single unit of a continuous variable [53].

Whilst logistic regression can be used to investigate the probability of an event happening or not it does not take account of the fact that events may take place over a period of time and an event taking place in the short term has different implications to an event that occurs some time further in the future. For example, if a cohort of people is followed up for a period of several years and the outcome of interest is death it would not be appropriate to give equal weight to a death that occurred a month after the start of the follow up period as to a death that may have occurred many years after initial data collection. A set of statistical techniques, called survival analysis, can be used to assess the probabilities of a binary outcome based on multiple categorical and/or continuous variables. The specific models presented in later chapters are Cox proportional hazard models. This method is based on Breslow's estimate of the baseline hazard function. The model output includes hazard ratios associated with the outcome variable for each category of continuous variables and or each unit change of a continuous variable.

The statistical analyses presented in Chapters 3, 4 and 5 were undertaken in SPSS (https://www.ibm.com/uk-en/analytics/spss-statistics-software). SAS (https://www.sas.com/en_gb/home.html) was used to undertaken the survival analysis presented in Chapters 6, 7 and 8.

Chapter 3: Mortality among inpatients with diabetes

Introduction

In England 3.32 million adults had diagnosed diabetes in 2019 and total diabetes prevalence is expected to rise to 4.68 million by 2030 [8,14]. It is understood that diabetes results in higher mortality with those with Type 1 diabetes having an age standardised relative risk of dying of 2.35 and those with Type 2 diabetes being 1.36 times more likely to die than the general population [55]. People with diabetes are also more likely to be admitted to hospital, stay in for longer and be re-admitted as an emergency [52,56,57]. A diagnosis of diabetes and/or hyperglycaemia has been associated with poorer outcomes from hospital admissions for cardiac conditions [58–60]. However, there is little understanding of hospital mortality among patients with diabetes across the full spectrum of secondary and tertiary care.

There is regular monitoring of hospital mortality by the NHS and private data analysis organisations to identify local variation and any outlier hospital trusts that may have exceptional mortality rates. Although this monitoring provides data for sub-categories of admissions, the identification of diabetes is limited to patients where diabetes was the primary reason for admission. Of the 15.0% of hospital beds occupied by people with diabetes in only 9.0% (representing 1.4% of hospital beds) was the patient admitted for diabetes specific reasons [61]. These diabetes specific admissions predominately comprise diabetic emergencies and are therefore skewed towards a minority of hospital admissions among people with diabetes with an over representation of younger patients and those with Type 1 diabetes. This study has therefore examined hospital mortality among hospital admissions in patients with recorded diabetes. It seeks to identify whether there is an additional risk of mortality after adjustment for case-mix among hospital admissions in patients with recorded diabetes, the vast majority of whom were admitted for non-diabetic reasons, and to identify the extent of any trust level variation which may be attributable to service delivery using a two year census of hospital admissions.

Methods

An extract of every hospital admission to an English hospital between 1st April 2010 and 31st March 2012 where the patient was less than 80 years old on admission was taken from Hospital Episode Statistics, a database that records every hospital admission funded by the National Health Service in England. Admissions were identified as relating to patients with diabetes if a code for diabetes (ICD-10 E10-E14) was included as a primary or secondary diagnosis. The primary and secondary diagnosis codes for the hospital admission were searched for a number of co-morbidities. These were used to calculate a modified Charlson index (see **Table 3.1** for definitions and scoring) [62,63]. Deprivation was measured using the Indices of Multiple Deprivation 2010 based on the patient's home address [64]. Method of admission was classified as elective, emergency or a transfer from another hospital trust. All admissions were classified into Healthcare Resource Group (HRGs) version 4 chapters [65].

Table 3.1: Modified Charlson score

Co-morbidity	ICD-10 codes identified in any diagnosis field	Score
Myocardial infarction	I21-I22	1
Congestive heart failure	I50	1
Peripheral vascular disease	I73.9, I71	1
Cerebrovascular disease	I60-I69	1
Dementia	F00-F03	1
Chronic pulmonary disease	J40-J47	1
Connective tissue disease	M30-M36, M05-M07, M10-M14	1
Ulcer disease	K25-K28	1
Mild liver disease	K70, K73, K74	1
Hemiplegia	G81, G82	2
Moderate or severe renal disease	N03-N16, N18-N19, N25	2
Any tumour	C00-C76	2
Leukemia or lymphoma	C81-C96	2
Moderate or severe liver disease	K72, I85	3
Metastatis solid tumour	C77-C80	6
AIDS	B20-B24	6

All regular hospital admissions (e.g. for chemotherapy treatments or dialysis) were excluded to remove bias resulting from repeats hospital admissions that relate to a specific treatment regimen and admissions relating to obstetrics (HRG chapter N) were excluded as they have the potential to obscure findings for women of child bearing age.

Statistical analysis

Differences in the characteristics of admission in patients with diabetes compared to those without diabetes were identified and the statistical significance of differences in proportions was tested using chi-squared tests. A binary logistic regression model containing all admissions with diabetes recorded was created. Death at the end of the hospital admissions was the dependent variable and age, sex, deprivation quintile, method of admission, modified Charlson score, HRG chapter and type of provider trust were included as explanatory variables. The resultant equation was used to calculate the odds of death for each admission which was converted into the probability of death. The probability of death for each admission with diabetes was summed for each provider trust (one or more NHS hospitals administered under the same management structure) to give the expected number of deaths. The observed number of admissions ending in death was divided by the expected number of admissions ending in death to give standardised mortality ratios comparing mortality among their admissions in patients with a diagnosis of diabetes to all admissions with diabetes included in the analysis for each hospital trust. This gave a measure of relative mortality compared to all admissions with diabetes recorded included in the analysis. Confidence intervals for the standardised mortality ratios were calculated using the Byar's method [66]. A separate model was created for admissions without diabetes to investigate whether the influence of case mix differed between admissions with and without a diagnosis of diabetes and to create a measure of relative mortality for all admissions without diabetes in the cohort.

The extent to which variation in mortality in admissions among patients with diabetes reflected patterns of general hospital mortality was investigated with comparisons with general measures of hospital mortality. The relationship between trust level mortality ratios for admissions with diabetes standardised to

all admissions with diabetes included in the analysis and the similar standardised mortality ratio for admissions without diabetes from this analysis, the Summary Hospital level Mortality Indicator (SHMI) produced by the NHS Information Centre and Hospital Mortality Standardised Ratio (HMSR) produced by Dr Foster Research Ltd was explored using Pearson's correlation co-efficient and linear regression models [67,68].

To assess the impact of diabetes in different specialities a separate binary logistic regression model was created that included admissions with and without diabetes for each HRG chapter. The dependent variable was whether the admissions ended in death and explanatory variables were age, sex, method of admission, modified Charlson score, type of hospital and whether the patient had a diagnosis of diabetes. The odds ratios associated with diabetes were converted to relative risks using the formula set out by Zhang and Yu [69]. These relative risks were used to calculate the number of additional deaths seen in patients with diabetes compared to those without diabetes by HRG chapter after standardisation for case mix in the two year period.

Each provider trust included in the analysis was classed as an acute teaching trust, a large acute trust, a medium acute trust or a small acute trust [70]. A binary logistic regression model was created with death as the dependent variable and whether the admission had diabetes recorded, age at the start of the admission, sex, method of admission, modified Charlson score, HRG chapter and type of trust as explanatory variables for each group of trusts to identify whether the adjusted odds of mortality associated with diabetes being recorded differed by the type of provider. To identify the additional risk of dying experienced in admissions among patients with diabetes compared to those without diabetes binary logistic regression models with death as the dependent variable were created for each provider trust. These models included whether the admission had diabetes recorded, age at the start of the admission, sex, method of admission, modified Charlson score, HRG chapter and type of trust as explanatory variables. The resultant odds ratios were converted to relative risks [69].

All analyses were undertaken in IBM SPSS 20.

Results

Between 1st April 2010 and 31stMarch 2012 there were 10,169,003 hospital admissions to 146 provider trusts that met the inclusion criteria. Of these 1,142,830 (11.2%) had diabetes recorded. Emergency admissions accounted for a greater proportion of admissions where there was a diagnosis of diabetes (75.8% vs 72.0% in those without diabetes, chi-squared=9573.602, df=2, p<0.005). Compared to those without diabetes, admissions among patients with a diagnosis of diabetes were more likely to be for HRG E (cardiac surgery and primary cardiac conditions), HRG K (endocrine and metabolic system) and HRG L (urinary system and male reproductive system), HRG D (Respiratory system) and HRG b (Eyes and periorbita) (chi-squared=465816.962, df=18, p<0.005). There were 169,999 deaths in hospital of which 36,662 (21.5%) were in admissions with diabetes recorded. Adjustment for age, sex, method of admission, HRG chapter and type of hospital trust reduced the crude odds ratio of dying from 2.207 (95% CI 2.182-2.233) to 1.137 (95% CI 1.123 – 1.151) (-2 log likelihood=308633.493, df=26, p<0.005). Adding the modified Charlson score to the case-mix adjustment further reduced the odds ratio to 1.065 (95% CI 1.052-1.079) (-2 log likelihood =1293894.81, df=31, p<0.005). This equates to a 6.32% greater risk of dying for admissions among patients with diabetes than would have been expected in similar admissions without diabetes recorded (2,316 more deaths over two years); alternatively, it equals 1.4% of all deaths in all admissions (with and without diabetes).

The results of the regression models exploring the different odds of mortality associated with the case mix factors in admissions among patients with diabetes recorded and separately among those without diabetes are shown in **Table 3.2**. Lower additional risks of death in admissions among patients with diabetes recorded compared to those without diabetes include older age and emergency admission or transfer from another trust. After adjustment for age, sex, method of admission, HRG chapter and co-morbidities there were no coherent deprivation gradients in the odds of death among admissions in patients with diabetes or in those without diabetes recorded (see **Table 3.2**, third and sixth columns of data).

Table 3.2: Results of regression models for admissions with diabetes and those without diabetes

		Admissions without diabetes recorded			Admissions with diabetes recorded		
		Adjusting for age, sex, method of admission reason for admission and type of trust Odds ratio (95% CI)	Adjusting for age, sex, method of admission reason for admission, type of trust and co-morbidities Odds ratio (95%CI)	Adjusting for age, sex, method of admission reason for admission, type of trust, co-morbidities and deprivation Odds ratio (95%CI)	Adjusting for age, sex, method of admission reason for admission and type of trust Odds ratio (95% CI)	Adjusting for age, sex, method of admission reason for admission, type of trust and co-morbidities Odds ratio (95%CI)	Adjusting for age, sex, method of admission reason for admission, type of trust, co-morbidities and deprivation Odds ratio (95%CI)
Age in years at start of admission		1.065 (1.064-1.065)	1.049 (1.048-1.049)	1.049 (1.049-1.050)	1.056 (1.055-1.058)	1.046 (1.045-1.047)	1.046 (1.044-1.047)
Sex	Male	1.225 (1.211-1.239)	1.181 (1.167-1.195)	1.181 (1.167-1.194)	1.046 (1.024-1.069)	0.995 (0.973-1.017)	0.994 (0.973-1.017)
	Female	-	-	-	-	-	-
Method of admission	Elective *	-	-	-	-	-	-
	Emergency	7.122 (6.941-7.308)	7.839 (7.639-8.045)	7.785 (7.585-7.990)	6.818 (6.458-7.198)	6.988 (6.619-7.378)	7.010 (6.638-7.402)
	Transfer	9.563 (9.193-9.948)	9.751 (9.369-10.149)	9.713 (9.331-10.111)	10.417 (9.380-10.976)	9.881 (9.127-10.696)	9.980 (9.125-10.698)
Healthcare Resource Group	A – Nervous system	3.045 (2.967-3.125)	2.414 (2.351-2.478)	2.423 (2.360-2.488)	2.023 (1.930-2.120)	1.813 (1.728-1.901)	1.813 (1.728-1.902)
	B – Eyes and periorbita	0.148 (0.114-0.191)	0.203 (0.157-0.263)	0.202 (0.156-0.262)	0.120 (0.072-0.199)	0.160 (0.096-0.267)	0.161 (0.097-0.267)
	C – Mouth, head, neck & ears	1.421 (1.360-1.484)	1.392 (1.332-1.455)	1.396 (1.335-1.459)	1.244 (1.139-1.360)	1.358 (1.241-1.485)	1.352 (1.236-1.480)
	D – Respiratory system	5.347 (5.232-5.465)	3.360 (3.286-3.435)	3.342 (3.268-3.417)	3.506 (3.381-3.636)	2.710 (2.612-2.812)	2.714 (2.615-2.816)
	E – Cardiac surgery and primary cardiac conditions*	-	-	-	-	-	-
	F – Digestive system	2.447 (2.389-2.507)	1.824 (1.780-1.869)	1.828 (1.784-1.874)	1.771 (1.699-1.847)	1.520 (1.457-1.586)	1.520 (1.457-1.587)
	G – Hepato-biliary and pancreatic system	4.230 (4.102-4.362)	3.048 (2.952-3.146)	3.048 (2.953-3.147)	3.237 (3.069-3.414)	2.457 (2.325-2.596)	2.463 (2.331-2.603)
	H – Musculoskeletal system	0.730 (0.706-0.755)	0.736 (0.711-0.761)	0.739 (0.715-0.765)	0.693 (0.652-0.736)	0.735 (0.691-0.781)	0.735 (0.691-0.782)
	J – Skin, breast & burns	1.281 (1.227-1.337)	1.023 (0.979-1.068)	1.027 (0.983-1.073)	0.977 (0.907-1.053)	0.948 (0.879-1.022)	0.945 (0.876-1.020)
	K – Endocrine and metabolic system	1.888 (1.771-2.013)	1.250 (1.171-1.335)	1.256 (1.177-1.341)	0.690 (0.641-0.743)	0.678 (0.629-0.730)	0.676 (0.628-0.729)
	L – Urinary tract and male reproductive system	1.576 (1.529-1.625)	1.067 (1.034-1.101)	1.072 (1.039-1.106)	1.394 (1.330-1.462)	1.144 (1.090-1.20)	1.146 (1.092-1.203)
	M – Female reproductive system	1.229 (1.149-1.313)	1.065 (0.996-1.139)	1.007 (1.000-1.144)	1.749 (1.487-2.059)	1.346 (1.140-1.590)	1.357 (1.149-1.602)

	P – Diseases of childhood and neonates	1.256 (1.141-1.383)	0.871 (0.791-0.960)	0.890 (0.808-0.980)	0.505 (0.303-0.843)	0.562 (0.337-0.938)	0.558 (0.334-0.932)
	Q – Vascular system	8.359 (8.101-8.626)	6.260 (6.062-6.465)	6.256 (0.6057-6.461)	4.239 (4.022-4.468)	4.008 (3.800-4.229)	3.989 (3.781-4.209)
	R – Radiology and nuclear medicine	3.244 (2.332-4.513)	2.242 (1.605-3.131)	2.270 (1.625-3.171)	2.972 (1.515-5.829)	2.356 (1.197-4.638)	2.367 (1.202-4.659)
	S – Haematology, chemotherapy, radiotherapy and specialist palliative care	3.260 (3.139-3.386)	1.599 (1.538-1.662)	1.614 (1.552-1.677)	1.737 (1.602-1.883)	1.173 (1.080-1.273)	1.169 (1.076-1.269)
	U – Undefined groups	2.736 (2.68-2.848)	2.698 (2.589-2.811)	2.709 (2.600-2.824)	2.311 (2.128-2.510)	2.117 (1.946-2.302)	2.110 (1.940-2.295)
	V – Multiple trauma, emergency medicine and rehabilitation	2.620 (2.455-2.796)	3.325 (3.112-3.552)	3.290 (3.077-3.517)	1.249 (1.028-1.517)	1.495 (1.227-1.821)	1.491 (1.223-1.818)
	W – Immunology, infectious diseases and other contacts with health service	1.715 (1.662-1.769)	1.469 (1.424-1.517)	1.473 (1.427-1.521)	1.651 (1.567-1.741)	1.523 (1.443-1.607)	1.526 (1.447-1.610)
Type of trust	Teaching trust *	-	-	-	-	-	-
	Large acute trust	0.994 (0.980-1.009)	1.091 (1.075-1.108	1.097 (1.081-1.114)	1.085 (1.054-1.117)	1.151	1.148 (1.114-1.182)
	Medium acute trust	0.967 (0.951-0.983)	1.064 (1.046-1.082)	1.075 (1.057-1.093)	1.103 (1.069-1.139)	1.183	1.178 (1.140-1.217)
	Small acute trust	0.956 (0.936-0.976)	1.083 (1.060-1.106)	1.104 (1.080-1.128)	1.132 (1.088-1.177)	1.239	1.228 (1.179-1.279)
Modified Charlson score	0	#	-	-	-	-	-
	1	#	2.765 (2.716-2.815)	2.736 (2.687-2.785)	#	2.142 (2.070-2.217)	2.142 (2.070-2.218)
	2	#	4.776 (4.684-4.868)	4.751 (4.661-4.844)	#	3.425 (3.305-3.550)	3.427 (3.306-3.551)
	3	#	6.871 (6.709-7.037)	6.798 (6.637-6.962)	#	4.597 (4.414-4.788)	4.594 (4.411-4.786)
	4	#	10.429 (10.104-10.764)	10.289 (9.968-10.621)	#	6.462 (6.141-6.801)	6.461 (6.139-6.801)
	5+	#	14.287 (14.022-14.557)	14.328 (14.061-14.599)	#	10.405 (10.015-10.811)	10.383 (9.993-10.788)
Deprivation	Most deprived	#	#	0.966 (0.951-0.983)	#	#	1.031 (1.000-1.063)
	2nd most deprived	#	#	0.921 (0.906-0.937)	#	#	1.040 (1.007-1.073)
	3rd most deprived	#	#	0.882 (0.866-0.897)	#	#	1.026 (0.992-1.062)
	2nd least deprived	#	#	0.857 (0.841-0.873)	#	#	1.020 (0.982-1.059)
	Least deprived *	-	-	-	-	-	-
Model statistics							
Chi-squared		260865.928	350657.189	349,437.245	34564.840	51835.903	51,606.386
Degrees of freedom		25	30	34	25	30	34
-2 log likelihood		1,113,588.32	1,023,797.06	1,017,863.26	285,951.203	268,680.140	267,668.274

P	<0.005	<0.005	<0.005	<0.005	<0.005	<0.005

* Indicates the reference group for the model, # indicates variable not included in model

The impact of having a diagnosis of diabetes on the odds of dying in hospital varied by HRG chapter: admissions due to HRG J (skin, breast and burns), HRG L (urinary tract and male reproductive system) and HRG M (female reproductive system and assisted reproduction) had the highest additional risk of death associated with diabetes. Admissions among patients with recorded diabetes admitted for HRG Q (vascular system) had a lower risk of dying than those without diabetes (361 (15.7%) fewer deaths over the two year period). The greatest numbers of additional deaths were in HRG chapters E (cardiac surgery and primary cardiac conditions) and L (urinary tract and male reproductive system) (see **Table 3.3**).

Table 3.3: Additional deaths by HRG chapter after standardisation for age, sex, method of admission, modified Charlson score and type of trust for patients with a diagnosis of diabetes

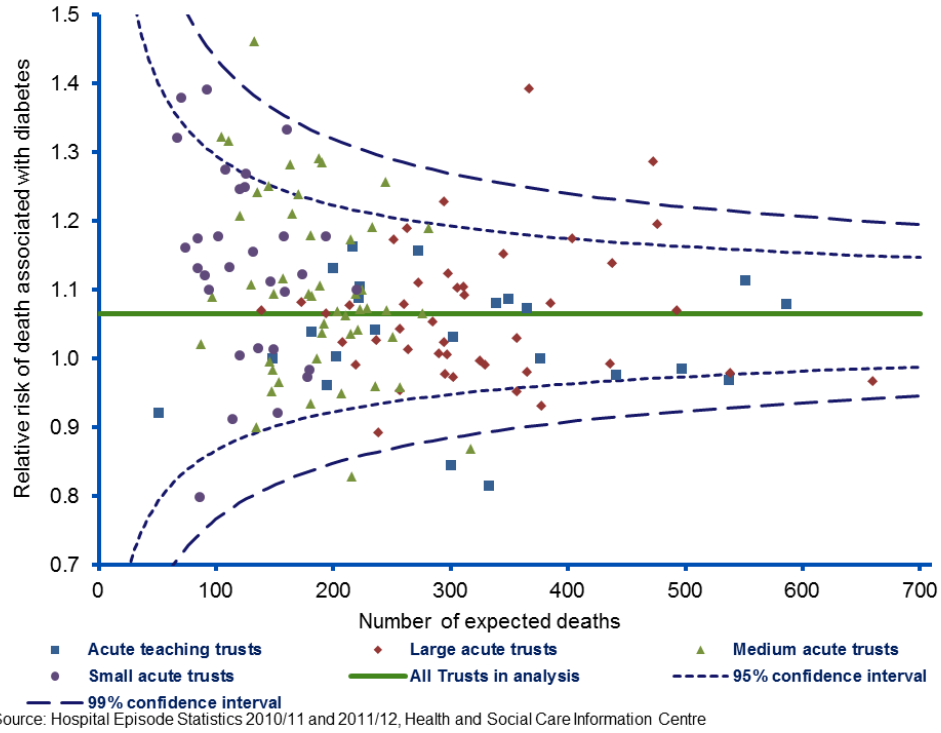
	Odds ratio (95% CI)	Total deaths	Additional deaths
			n (%)
A - The nervous system	0.978 (0.938-1.02)	3,008	-63 (-2.11%)
B - Eyes and periobita	1.104 (0.613-1.989)	15	2 (10.42%)
C - Mouth, head, neck & ears	1.221 (1.108-1.345)	574	126 (21.94%)
D - Respiratory system	1.002 (0.978-1.027)	9,355	19 (0.21%)
E - Cardiac surgery and primary cardiac conditions	1.182 (1.141-1.225)	4,825	866 (17.95%)
F - Digestive system	1.029 (0.994-1.065)	4,564	130 (2.85%)
G - Hepato-biliary and pancreatic system	1.043 (0.988-1.1)	2,134	89 (4.16%)
H - Musculoskeletal system	1.221 (1.148-1.3)	1,385	305 (22.01%)
J - Skin, breast and burns	1.3 (1.193-1.415)	844	251 (29.72%)
K - Endocrine and metabolic system	0.674 (0.613-0.742)	869	-280 (-32.23%)
L - Urinary tract and male reproductive system	1.288 (1.23-1.349)	2,895	822 (28.38%)
M - Female reproductive system	1.262 (1.042-1.528)	158	41 (26.09%)
P - Diseases of childhood and neonates	1.337 (0.795-2.248)	15	5 (33.67%)
Q - Vascular system	0.836 (0.794-0.88)	2,303	-361 (-15.68%)
R - Radiology and nuclear medicine	1.386 (0.643-2.986)	9	3 (37.99%)
S - Haematology, chemotherapy, radiotherapy and specialist palliative care	0.917 (0.843-0.998)	720	-58 (-8.08%)
U - Undefined groups	0.985 (0.902-1.075)	703	-11 (-1.53%)
V - Multiple trauma, emergency medicine and rehabilitation	0.853 (0.691-1.053)	108	-16 (-14.43%)
W - Immunology, infectious diseases and other contacts with health services	1.226 (1.163-1.293)	2,120	473 (22.33%)
All HRG chapters	1.065 (1.052-1.079)	36,622	2316 (6.32%)

Note: Sum of excess deaths split by HRG do not sum up to total excess deaths due to rounding.

There were significant differences in the odds ratio of death associated with a diagnosis of diabetes by the type of provider trust (1.029 95% CI 1.001-1.058 for acute teaching trusts, 1.049 (95% CI 1.029-1.069) for large acute trusts, 1.097 (95% CI 1.071-1.124) for medium acute trusts and 1.128 (95% CI 1.087-1.171) for small acute trusts). When trust level mortality among admission in patients with recorded diabetes was standardised to mortality among admissions for patients in the same trust without diabetes (taking account of age, sex, co-morbidities, deprivation, method of admission and HRG chapter) there were six (4.1%) trusts above and nine (6.2%) trusts below the 95% confidence interval. Using this measure mortality in admissions for patients with recorded diabetes was

significantly lower than inpatients without recorded diabetes in four (2.7%) trusts (see **Figure 3.1**).

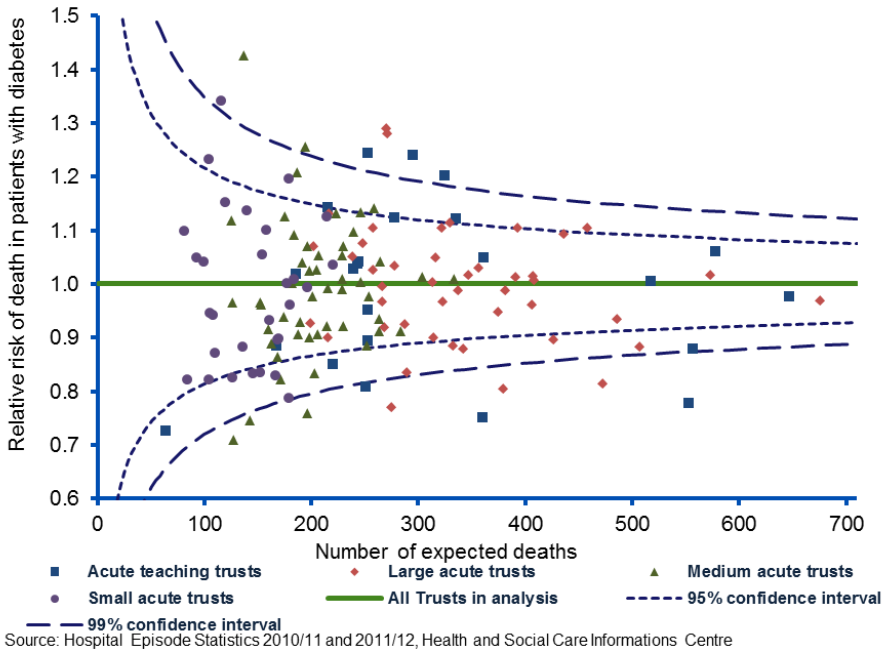
Figure 3.1: Trust level standardised mortality ratio of admissions among patients with diabetes compared to patients without diabetes in the same trust



Source: Hospital Episode Statistics 2010/11 and 2011/12, Health and Social Care Information Centre

There was greater variation in the trust level mortality ratios for admissions in patients with recorded diabetes standardised to all admissions among patients with recorded diabetes across the 146 trusts in the analysis. 16 (11.0%) trusts were above and 24 (16.4%) trusts were below the 95% confidence interval (see **Figure 3.2**). There was a positive correlation between this standardised diabetes mortality ratio and the comparable ratio for admissions without recorded diabetes included in this analysis ($r=0.615$, $p<0.005$); there were similar correlations with both of the published standardised hospital mortality ratios SHMI ($r=0.677$, $p<0.005$) and HMSR ($r=0.533$, $p<0.005$). These measures of general hospital mortality explained 37.4%, 39.6% and 32.9% of the variation respectively ($F=87.729$, $p<0.005$, $F=96.146$, $p<0.005$ and $F=71.961$, $p<0.005$).

Figure 3.2: Relative risk of death for admissions among patients with diabetes in each trust compared to all admissions among patients with diabetes in the analysis



Source: Hospital Episode Statistics 2010/11 and 2011/12, Health and Social Care Informations Centre

Discussion

After adjustment for case mix, admissions among patients with recorded diabetes were 6.3% more likely to die during a hospital stay than those without diabetes recorded. There was an adverse impact of diagnosed diabetes unexplained by other presently recognised case-mix factors. This equates to approximately 2,300 additional deaths per year in England. These deaths represent one in sixteen of the deaths in hospital among patients with diabetes, one in sixty (1.4%) of all hospital deaths and approximately 10% of the estimated 22,000 excess deaths among people with diabetes each year in England [55].

The additional risk of death found in admissions among patients with diabetes (5.6%) is lower than the additional risk of all-cause mortality for people with diabetes (40%) found by a study of all deaths among the 1.9 million people included in the National Diabetes Audit 2009/10 [55]. This is to be expected as the National Diabetes Audit analysis compared mortality among those with diabetes to the general population whereas the comparable population in this study is at a much greater risk of dying irrespective of their diabetes status. In

addition, this analysis includes a more comprehensive case-mix adjustment, in particular assessment of co-morbidities that have a significant impact on the risk of death. A ten year study of hospital mortality in a tertiary setting in Greece found that patients with Type 2 diabetes had a mortality rate 28% higher than patients without diabetes [71]. The unadjusted additional risk of death among inpatients with diabetes in this English analysis was similar to that found in a US study of mortality among inpatients with diagnosed diabetes, hyperglycaemia without a diagnosis of diabetes or normoglycaemic patients [72]. However, adjustments for case mix were not included in these studies so it is difficult to assess the comparative independent impact of a diabetes diagnosis on hospital mortality. This analysis found that adjustments for case mix substantially reduced the crude odds of dying associated with a diagnosis of diabetes.

This analysis did not find coherent deprivation gradients in the risk of death for admissions among patients either with or without diabetes. The National Diabetes Audit 2010/11 found clear deprivation gradients in all-cause mortality; people with diabetes living in the most deprived fifth of neighbourhoods had 37% greater odds of dying compared to those in the least deprived quintile [55]. Thus, although there is a deprivation gradient in the prevalence of diabetes [14], these inequalities are not exacerbated by hospital care and a diagnosis of diabetes has a stronger influence on hospital mortality than the patient's social background. Amongst admissions in patients with recorded diabetes the elderly, males and those admitted as an emergency had the smallest additional risks of dying in hospital. These are categories which are generally associated with the highest risks of in-hospital death. For admissions with recorded diabetes, however, the greatest additional risks were in admissions that would generally have low risks of death in hospital; these findings suggest an influence of diabetes on hospital mortality that partially overrides the usual inpatient mortality risk factors.

After adjustment for case-mix the additional risk of dying associated with a diagnosis of diabetes is significantly higher in medium and small provider trusts. This suggests that factors relating to the organisation and delivery of care may influence the risk of dying in hospital. When all trusts are analysed individually the extent of variation in the additional risk of death associated with a diagnosis

of diabetes there are approximately twice the number of trusts outside the confidence intervals than would be expected. The trust level variation is even greater when mortality among admissions in patients with diabetes are compared to similar admissions across England is considered. The significant correlation between general hospital mortality measures and mortality in admissions among patients with diabetes standardised across England means that approximately a third of the trust level variation is associated with differences in all-patient mortality between provider trusts. The fact that the measure of mortality among inpatients without diabetes and the general measures of inpatient mortality show a similar relationship with mortality among inpatient with diabetes supports the reliability of this finding. However, approximately half of the local level variation remains unexplained suggesting local differences in diabetes care may be responsible.

The additional risk of death varied according to the reason for admission. Admissions for cardiac disease and surgery or urinary tract disease and surgery showed the highest number of additional deaths. There is a large literature on the relationship between blood glucose levels and outcome from acute cardiac events [58–60]. However, the National Diabetes Inpatient Audit 2011 showed that, on average, inpatients with diabetes had target blood glucose control on only four out of seven days [61]. The concentration of additional deaths among inpatients admitted for urinary tract disease is likely to reflect the increased prevalence of chronic kidney disease among people with diabetes and their higher mortality on dialysis [73].

By analysing over one million hospital admissions where diabetes was recorded this study provides a comprehensive assessment of in-hospital mortality among patients with diabetes. The reliability of the findings is enhanced by the use of death as the outcome measure because it is not associated with recording biases. However, the measurement of mortality in this study is limited to deaths in hospital and does not include deaths that may occur shortly after discharge. Unlike some measures of hospital mortality, deaths associated with terminal illness have not been excluded so it is not legitimate to compare these findings directly with other commonly published rates. It is also possible that local provision and organisation of palliative care, in particular care for people with

multi-morbidities will explain some of local variation in the additional mortality found among hospital admissions in patients with diabetes. Nonetheless, because the same analysis was applied to admissions for patients with and without recorded diabetes the deductions about the impact of diabetes are reliable.

This analysis relies on discharge coding to identify patients that have diabetes. There are clear incentives for hospitals to ensure the accurate coding of long term conditions such as diabetes in the Payments for Results system. However, scepticism about the reliability Hospital Episode Statistics in identifying patients with diabetes persists. A recent study of hospital admissions among a cohort of 1.6 million people with diagnosed diabetes found that there was under recording of diabetes as a discharge diagnosis. However, for patients in whom diagnosed diabetes was not included in the discharge coding the length of stay, day case listing and emergency re-admissions were similar to those for patients without diabetes whereas they were markedly different in patients with recorded diabetes [52]. This suggests that patients with diabetes not recorded in discharge coding have hospital experiences similar to their peers without diabetes. It is therefore plausible that this study underestimates the number of admissions and over estimates the additional risk of death among the totality of admissions among patients with diabetes. Coding practices mean that it is not possible reliably to identify the type of diabetes and treatment regimen, duration of diabetes, bio-chemical markers and specific cause of death are is not recorded in HES. As a result, the scope to assess inpatient mortality by sub-group and report cause specific mortality is limited.

This study has assessed the current extent and characteristics of hospital mortality in admissions among patients with recorded diabetes across the full spectrum of secondary and tertiary care in England. It suggests a diabetes specific effect. Further research should consider the cause of death among inpatients with diabetes and, in light of the findings that the additional risk of dying is significantly higher in smaller non-specialist trusts, explore the associations between healthcare organisation and delivery and mortality.

Update since publication

A recent literature review has not identified any similar studies that consider mortality among inpatients with diabetes across the full spectrum of healthcare. The Summary Hospital-level Mortality Indicator (https://digital.nhs.uk/data-and-information/publications/ci-hub/summary-hospital-level-mortality-indicator-shmi) continues to be published by NHS Digital. The figures now report on a rolling 12-month period with monthly updates. This provides a timely assessment of mortality for people admitted to hospital for diabetic specific causes but the information and understanding of the full pattern of hospital mortality for people with diabetes remains limited.

Chapter 4: The development of a national audit of foot care for people with diabetes: Pilot work for the National Diabetes Foot Audit

Introduction

Increasing awareness of the size of the clinical and economic burden posed by disease of the foot in diabetes has meant that attempts to improve outcome have become a clinical priority. However, improvement in clinical care is dependent on knowledge of the effectiveness of current practices. Such insight will lead to recognition of differences in clinical outcome, where they exist, and this in turn will help identify key aspects of best practice, both clinically and administratively. These developments are, however, dependent on the existence of reliable measures of the structures, processes and outcomes of routine care in different clinical services. Without such measures, clinicians are to a large extent unaware of both the effectiveness of their own practice and of the changes that could be made to improve it.

Guidance exists on the identification, prevention of risk and management of diabetic foot disease in England [74–76] and elsewhere [77,78] but there are no data to demonstrate either how widely this guidance is adopted or for assessing its impact. Hitherto, the measure which has been most widely used is the incidence of amputation, and wide variation has been shown in the amputation rates across England [79] and in other countries [80] but the incidence of amputation is a measure which is acknowledged to require careful interpretation. Variation has also been reported in the incidence of hospital admissions for diabetic foot disease in England [81] and one formal prospective study has reported quite large differences in practice and clinical outcome between 14 specialist centres throughout Europe [82]. These variations in outcome imply geographical inconsistency in the quality of care provided and may reflect differences in either the approach to ulcer management or service organisation, both within countries and between them.

This study formed part of an initiative to develop and test a dataset and data collection methodology with the aim of creating an audit tool that could be used in any setting to assess diabetic foot service provision against current guidelines. The focus of this report is on the development of a measurement methodology relating to the management of active ulceration.

Methods

A national working group was established as part of the National Diabetes Audit programme in England and Wales [83] to consider measures for the assessment of different aspects of the pathway of care of disease of the foot in diabetes. These included details of the structure, process and outcomes of care. In order to audit the process of management of active ulceration, an email invitation was sent in June 2011 to representatives of specialist foot care services known to NHS England, inviting them to complete questionnaires on all people presenting will active ulceration of the foot over a three month period. If an individual had more than one lesion, one – assessed to be the largest or most clinically significant – was selected as the index ulcer.

A trial dataset was created following discussion within the working group, and comprised questions on the following topics:

(a) Details of people with foot ulcers:
demographics, postcode to allow assessment of social deprivation, diabetes type and duration, previous use of podiatry and receipt of foot protection advice, and previously determined foot risk score determined by their usual carer

(b) Details of the index ulcer:
classification and score derived using the SINBAD system which is a six point score based on the site, depth and area of the ulcer and the presence of infection, ischemia and neuropathy (see **Table 4.1** for details) [84], time and date of first presentation with the index ulcer to any healthcare professional, time and date of assessment by the specialist multi-disciplinary foot team (MDT) and whether the ulcer developed during a hospital admission

(c) Outcomes of the index ulcer at six and twelve months after presentation to the specialist MDT: date of ulcer healing if within 365 days, time to healing, amputation, hospital admission, death

(d) Well-being and function:

People included in the study were asked at presentation and at latest review to complete an EQ5D–3L [85] questionnaire, including assessment of current well-being and function.

After all data had been submitted, semi-structured telephone interviews were conducted with a representative of each unit and an attempt was made to identify common themes. The result of this feedback was used in conjunction with an assessment of data quality to devise a refined audit dataset and data collection methodology.

Statistical analysis

Statistical significance was calculated using chi-squared tests for categorical variables, t-tests for the difference in means between two groups and one-way analysis of variance for differences in continuous variables between categories. A step-wise binary regression model was created to assess the relative independent impact of demographic and ulcer characteristics on the chance of the ulcer healing within 12 and 24 weeks. Although the healing data was collected as continuous time to event data it was converted into dichotomous variables for analysis and logistic regression was undertaken to test the use of the methods that would be applied to the revised data to be collected in the national audit programme. The coefficients for healing at 24 weeks were used to identify the personalised probability of ulcer healing of each person in the study. For each participating centre that reported more than one healed ulcer the sum of these probabilities was compared with the actual number of peoples with healed ulcers to provide a standardised case-mix adjusted healing ratio (SHR). Byar's method was used to calculate 95% and 99% confidence intervals for each SHR [66]. Data analysis was performed in Excel 2007 and IBM SPSS 21.

Results

Clinical characteristics and outcomes

Demographic and ulcer characteristics at presentation

Twenty three units provided data on the process of management of 652 peoples newly presenting with a diabetic foot ulcer. The mean age was 65.2 (SD 14.3) years and 451 (69.2%) were male (**Table 4.1**). 89 (13.7%) had Type 1 diabetes, 550 (84.4%) had Type 2 diabetes and 13 (2.0%) had genetic, other or unknown type of diabetes. The majority (581 or 89.1%) were from White ethnic groups. It was possible to derive a deprivation score from postcodes for 601 (92.2%) people; 185 (30.8% of 601) lived in the most deprived quintile of areas in England while 86 (14.3%) lived in the least deprived quintile.

Table 4.1: Ulcer SINBAD score at presentation to the multi-disciplinary foot team

	N (%)
Site - Ulcer on midfoot or hind foot (rather than forefoot)	158 (24.2%)
Ischaemia - Clinical evidence of reduced blood flow	247 (37.9%)
Neuropathy – Protective sensation lost	548 (84.0%)
Bacterial infection – Present	322 (49.4%)
Area – Ulcer equal to or greater than 1cm^2	318 (48.8%)
Depth – Involving the muscle, tendon or deeper	168 (25.8%)
SINBAD score 0	23 (3.5%)
SINBAD score 1	111 (17.0%)
SINBAD score 2	172 (26.4%)
SINBAD score 3	162 (24.8%)
SINBAD score 4	110 (16.9%)
SINBAD score 5	64 (9.8%)
SINBAD score 6	10 (1.5%)

Each ulcer is allocated one point for each aspect of the score

617 (94.6%) of the population had a valid pre-ulcer risk score recorded of whom 453 (73.4%) had been assessed to be high risk, 134 (21.7%) increased risk and 30 (4.9%) low risk. 605 (92.8%) had previously been seen for foot protection advice by one or more healthcare professionals: podiatrist (71.8%), general practitioner (27.1%), diabetologist (24.5%) practice nurse (17.2%), solely or in combination. People previously identified as being at high risk of future ulceration were more likely to have received foot protection advice or care (97.6% high risk, 91.8% increased risk, 86.7% of peoples at low risk (x^2 15.058, p=0.001).

Valid data for time of first presentation to a healthcare professional and of assessment by the multi-disciplinary foot team was available for only 460 (70.6%) of cases. Therefore it was not possible to assess the proportion of people that accessed the MDT within 24 hours of first presentation, as recommended by UK guidance [76]. For people with both a valid date of first presentation to any healthcare professional and a date of first assessment by the MDT, 280 (60.9%) reached the MDT in $\leq$2 days. 346 (53.1%) people had an index ulcer with a SINBAD score of $\geq$3, which has previously been associated with worse prognosis. Twenty six (4.0%) people developed their ulcers whilst a hospital inpatient.

Outcomes

Valid outcome data were recorded for 541 (83.0%) people. 92 (21.1%) people were admitted to hospital for ulcer management. 267 (49.4% of 541) index ulcers healed within 12 weeks increasing to 351 (64.9%) at 24 weeks. The median time to healing was 63 days (range 5–359). There was no difference in the mean age of people whose ulcers healed when compared with those that didn't (65.8 versus 64.5 years, t=1.075, p=0.282 at 12 weeks and 66.6 versus 64.4 years, t=1.804, p=0.076 at 24 weeks). The proportion of people with a SINBAD score of 3 or greater seen by the MDT within two days was similar to those who took longer (53.2% vs 53.9% chi-squared=0.028, p=0.866). Longer healing times were associated with higher SINBAD scores at presentation (**Table 4.2**).

Table 4.2: Time to healing by SINBAD score

SINBAD score	Healed within one year N (%)	Healed within 12 weeks N (%)	Healed within 24 weeks N (%)	Time to healing median (range)
0	17 (89.5)	11 (57.9)	16 (84.2)	40 (13-196)
1	89 (89.0)	70 (70.0)	86 (86.0)	47 (6-343)
2	120 (81.1)	83 (56.1)	103 (69.6)	57 (7-359)
3	92 (69.7)	63 (47.7)	80 (60.6)	72 (14-333)
4	54 (64.3)	28 (33.3)	48 (57.1)	87 (5-275)
5	21 (41.2)	10 (19.6)	16 (31.4)	108 (27-309)
6	4 (57.1)	2 (28.6)	2 (28.6)	160 (34-267)
	Chi-square = 69.219 p<0.005	Chi-square = 48.315 p<0.005	Chi-square = 56.580 p<0.005	

Univariate analysis showed that there were no significant differences in the incidence of ulcer healing by personal characteristics (sex, ethnic group, deprivation, previously defined foot risk). The incidence of healing was no greater if the time from first assessment by a healthcare professional to assessment by the MDT was >2 days. Healing at both 12 and 24 weeks was less likely if the ulcer site was on the mid- or hind-foot, had a larger area ($\geq$1 cm^2) or greater depth (involving the muscle, tendon or bone) or if there was clinical evidence of peripheral arterial disease (PAD). Bacterial infection was associated with lower healing rates at 12 weeks but the difference was not statistically significant at 24 weeks whilst the loss of protective sensation was not associated with differences in healing (see **Table 4.3**).

Table 4.3: Univariate assessment of ulcer healing by demographic and ulcer characteristics

		12 weeks		24 weeks	
		N (%)	p	N (%)	p
Sex	Males	179 (48.4)	0.505	241 (65.1)	0.855
	Females	88 (51.5)		110 (64.3)	
Type of diabetes	Type 1	34 (52.3)	0.877	39 (60.0)	0.579
	Type 2	229 (48.9)		306 (65.4)	
	Other	4 (50.0)		6 (75.0)	
Ethnic group	White	231 (48.2)	0.500	307 (64.6)	0.565
	Asian	20 (60.6)		25 (75.8)	
	Black	5 (50.0)		6 (60.0)	
	Other	6 (60.0)		6 (60.0)	
Deprivation	Most deprived	84 (51.2)	0.924	110 (67.1)	0.917
	2nd most deprived	44 (45.8)		59 (61.5)	
	3rd most deprived	52 (51.5)		66 (65.3)	
	2nd least deprived	40 (50.0)		52 (65.0)	
	Least deprived	28 (48.3)		39 (67.2)	
Foot risk prior to ulcer	High	184 (49.1)	0.697	232 (61.9)	0.026
	Increased	60 (53.1)		83 (73.5)	
	Low	13 (54.2)		19 (79.2)	
Time to see MDFT	Within 2 days	143 (43.8)	0.012	176 (67.4)	0.160
	Longer than 2 days	114 (54.8)		160 (61.5)	
SINBAD score elements	Forefoot	221 (53.0)	0.002	289 (69.3)	<0.005
	Mid- or hind-foot	46 (37.1)		62 (50.0)	
	At least one pulse palpable	193 (55.3)	<0.005	254 (72.8)	<0.005
	Clinical evidence of reduced blood flow	74 (38.5)		97 (50.5)	
	Protective sensation intact	35 (41.2)	0.101	54 (63.5)	0.776
	Protective sensation lost	232 (50.9)		297 (65.1)	
	No bacterial infection	162 (58.5)	<0.005	195 (70.4)	0.006
	Bacterial infection present	105 (39.8)		156 (59.1)	
	Ulcer less than 1cm^2	162 (57.8)	<0.005	208 (73.2)	<0.005
	Ulcer greater or equal to 1cm^2	105 (40.9)		143 (55.6)	
	Ulcer involving skin and subcutaneous tissue	230 (56.2)	<0.005	290 (70.9)	<0.005
	Ulcer involving the muscle tendon or deeper	37 (28.0)		61 (46.2)	

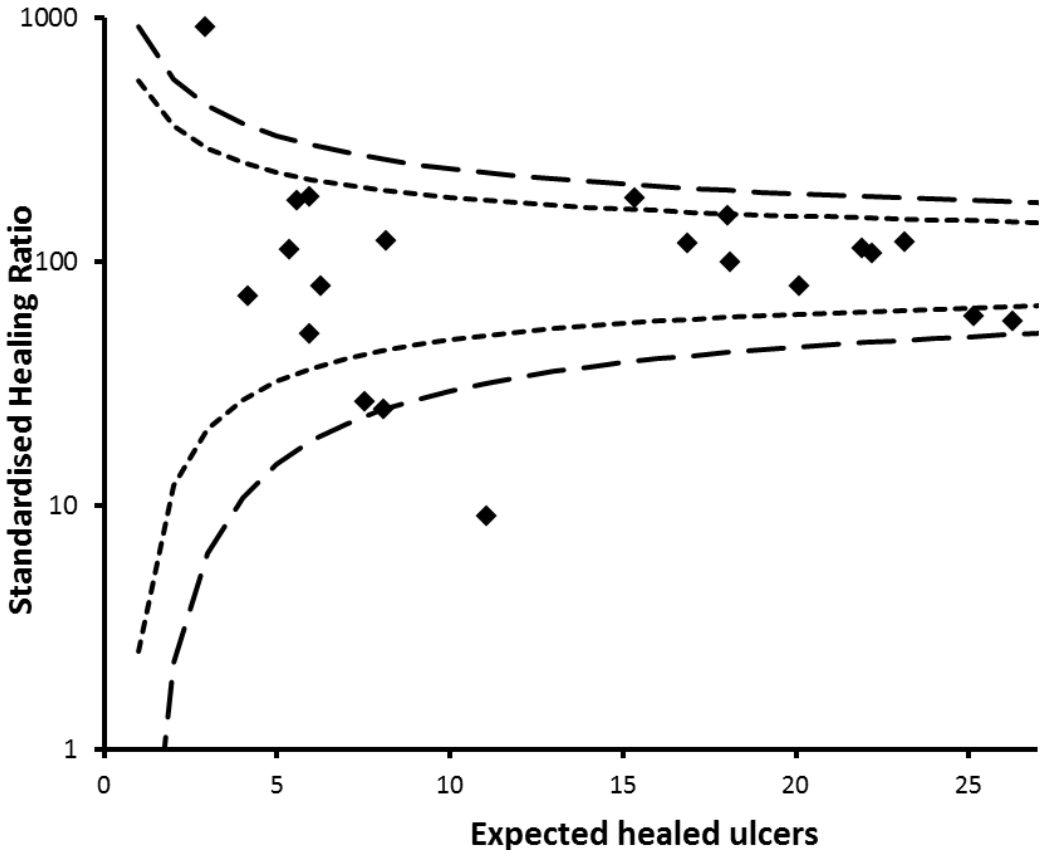
The multivariate regression model showed that mid- or hind-foot location, greater depth or accompanying clinical evidence of PAD were associated with reduced likelihood of healing (**Table 4.4**). Age, sex, type of diabetes, deprivation, risk assessment prior to ulceration and time to MDT assessment were not independently associated with healing.

Table 4.4: Binary logistic regression models

		Healed at 12 weeks Odds ratio (95% CI)	Healed at 24 weeks Odds ratio (95% CI)
SINBAD score elements	Mid- or hind-foot (rather than forefoot)	0.625 (0.394-0.993)	0.527 (0.329-0.844)
	Clinical evidence of reduced blood flow (rather than at least one palpable pulse)	0.471 (0.312-0.709)	0.356 (0.233-0.544)
	Ulcer involving the muscle, tendon or deeper (rather than just skin and subcutaneous tissue)	0.313 (0.195-0.503)	0.334 (0.210-0.531)
Model statistics (-2 log likelihood, p)		579.868, <0.005	524.174, <0.005

The regression model finding that ulcer site, depth and the presence or not of clinical evidence of PAD were independent determinants of healing enabled standardised healing ratios (SHRs) to be calculated for 21 of the 23 participating clinics. Three (14.9%) units had a SHR above the 95% confidence interval and five (23.8%) had a SHR below the 95% confidence interval (see **Figure 4.1**).

Figure 4.1: Funnel plot of standardised healing ratios showing the scatter observed between participating centres



EQ5D-3L

A valid self-assessment of well-being and function on the EQ5D-3L visual analogue scale was reported for 618 (94.8%) people at presentation but for only 378 (58.0%) at the time of outcome recording; complete data were available for 376 (57.7%). At presentation the mean self-reported assessment of health was 58.3 (SD 21.8). At outcome recording the mean score was 65.0 (SD 22.9). Assessments of well-being improved by a mean 5.0 points (SD19.7) if the ulcer had healed and by a mean 1.0 point (SD 31.6) if it had been resolved by amputation. People with an unhealed ulcer at latest follow-up reported a mean 7.05 (SD16.8) point deterioration in well-being ($F=6.734$, $p<0.005$).

Feedback from participating units

Common themes emerging from interviews with participating centres were difficulty (i) with precise recording of the date and time of first presentation, (ii) in defining the identity of professionals who had undertaken earlier foot

screening (iv) in determining the allocated pre-ulcer risk score, and (iv) in ascertaining who had cared for the ulcer prior to first specialist assessment. All but one of the participants found the SINBAD grading easy to use and useful in clinical documentation. There were mixed views on the EQ-5D questionnaire. Some found it very easy to administer but others found it difficult to explain that it was a 'holistic' view of current health status and not just concerned with the presenting problem. It was also difficult to use if English was not the person with diabetes's first language. Whilst the audit record took less than ten minutes to complete, most sites reported that this presented too much of a burden in busy clinics, with the result that the ulcers reported did not always constitute a consecutive series and therefore potentially introduced a bias in the data collected. All participants emphasised the need to minimise the burden of data collection.

Discussion

The data collected in this study not only lay a foundation for recommending an operational audit dataset but also provide some insight into the current outcomes of the management of diabetic foot ulcers by specialist teams in England. About half (49.4%) of ulcers reported had healed within 12 weeks. The characteristics of the people included in this analysis are similar to those at the English centre that originally validated the SINBAD score, though the median healing times at 12 and 24 weeks reported here are slightly lower [84]. This difference may reflect clinical advances over the intervening ten years, but may also reflect a change towards more prompt and less selective referral to specialist services in UK, as recommended in current guidance. The ulcer healing rate is also broadly comparable with other UK and European studies: foot ulcers healing without amputation at 12 months have previously been reported to be 65% percent by 12 months in 194 peoples managed in one of two centres [86], 65.7% of 449 peoples in a single centre study from UK [87] and 64% in the Eurodiale study [82]. It should be noted that the data used in the present study were provided by volunteer units and that all published data also derive from those with a specialist interest. In the absence of information that is routinely collected in a representative cross section of services, it is not possible to determine the extent to which these findings reflect outcome in general.

People likely to have the poorest outcomes (eg those presenting as an emergency and requiring immediate surgical intervention, vulnerable people who are not able to attend specialist centres) are often not managed by specialist foot care teams.

This study has found that some presenting ulcer characteristics (area, clinical evidence of arterial disease and site) are clearly associated with healing but personal and demographic characteristics are not. Although it is well known that diabetic foot disease and amputation, in particular, are more prevalent amongst White ethnic groups as well as among males living in deprived areas [55,88,89] we found no link in this study between outcome and either ethnic group or social deprivation. The lack of relationship between healing and deprivation was also reported earlier in a single centre cohort in UK of similar size [90]. This discordance in relationships may be because the greatest impact of race and deprivation (in a country like England, with universal access to health care services) is on ulcer onset, whereas the state of the ulcer at presentation is the more important determinant of healing. It is similarly not surprising that neuropathy was not associated with healing rates because it, too, is likely to be a risk factor primarily for ulcer onset.

The results of this study further validated the SINBAD score at ulcer presentation as a reliable assessment of ulcer severity in that it was linked to measures of outcome; ulcers with a SINBAD score of three or greater are both less likely to heal, and to take longer when they do. It is probable that elements of the SINBAD score override the time to first multi-disciplinary foot team visit as an outcome predictor. This, together with difficulties in acquiring accurate data on ulcer duration at the time of referral, would explain the lack of an association between ulcer duration and clinical outcome when compared with previous observations [90,91] – although it should be noted that these earlier observations were based solely on those with neuropathic ulcers and that there are no equivalent data for unselected populations. Nevertheless, it is very likely that delayed referral is a direct cause of worse ulcer state at first specialist assessment and the implication is that improved outcome reflects not only a reduction in the time to assessment by a MDT but also earlier implementation of customised management of particular ulcer types. This would resonate with

clinical experience. The use of a case-mix adjusted healing ratio (SHR) was explored in this pilot and the findings suggest that this approach could be used by units to benchmark their performance against peer services –whether in UK or other countries.

Assessment of quality of life is multi-dimensional and dependent on many factors which may be outside the scope of the healthcare setting being considered. It is particularly complex in a patient population, such as the one in this analysis, with a high prevalence of multiple and often severe co-morbidities [92,93]. This is reflected in the low proportion of people with valid data to assess change in quality of life. However, the improvement in quality of life reported by people whose ulcer healed and the deterioration in quality of life reported by people whose ulcer remained unhealed serves to highlight the health burden created by the delayed healing that typifies the condition and confirms earlier reports from large multicentre studies [94,95]. The small improvement in reported well-being by people who underwent an amputation is similar to other reports [96] and supports the view that, where appropriate, amputations can represent positive treatment for people with diabetic foot disease.

The primary purpose of this study, however, was not to study outcome in a cohort of people presenting with foot diseases but to pilot a process for measuring the management of diabetic foot ulcers by specialist teams. It successfully tested a provisional methodology in 23 units across England, even though the users found some aspects of recording data onerous – which suggests that the questions used would be difficult to implement in routine practice. The lack of follow up data on a significant minority of people can be in part attributed to the difficulty in identifying outcomes after people have been discharged from the specialist unit. In England and Wales, however, it would be feasible to reduce the imposed recording burden by using the unique national NHS number to link to data stored by the National Diabetes Audit. These data include demographics (age, sex, ethnic group, deprivation score), diabetes management characteristics (type and duration of diabetes, HbA1c, blood pressure, cholesterol, estimated glomerular filtration rate; foot examination), hospital admissions for the management of diabetic foot disease, amputations and mortality thereby ensuring that some outcome data for all people included

in the audit irrespective whether locally collected outcome data were provided. This would markedly reduce the burden of local data collection from twenty five fields to ten and yet permit reliable measurement of case-mix adjusted performance against current guidelines, as well as linkage between aspects of performance and measures of clinical outcome. The inclusion of foot disease in the national programme of audits should make it easier for teams to access local audit support which will be vital to ensuring robust local data collection. Nevertheless, it is clear that the number of items that need to be collected by clinicians working in busy routine practice must be further reduced if the data recorded are to be both complete and reliable – especially if the plan is that audit data are collected for all new referrals, without selection. The reduced data-set currently being considered is shown in **Table 4.5**.

Table 4.5: Recommended measurement dataset for local recording in a specialist foot care clinic

Identifiable information to allow linkage to core National Diabetes Audit, data on hospital admissions and deaths	NHS number
Referral for specialist assessment Time from first presentation to a health care professional to time of first assessment by a member of the MDT	Less than 2 days 2 days or more but less than 2 weeks 2 weeks of more but less than 2 months 2 months or more
Ulcer type and severity at presentation	SINBAD classification and score at first expert assessment Whether there is evidence of charcot neuroarthropathy
Outcomes at 12 and 24 weeks after first assessment by the multi-disciplinary foot team	Whether the person is alive an ulcer free

Participating centres

Aintree Hospital, Arrowe Park and Clatterbridge Hospitals, Bradford Hospitals Rapid Access Foot Ulcer Clinic, Ipswich Hospital, King's Mill Hospital, Newcastle Diabetes Centre, North Middlesex University Hospital, Northampton General Hospital and Battle House, Northern General and Royal Hallamshire Hospitals, Poole Hospital, Royal Devon and Exeter Hospital, Royal Free Hospital, Royal Liverpool and Broadgreen University Hospitals, Royal United Hospital, Salford Royal Hospital, Southport and Ormskirk Hospital, St Helens and Knowsley Teaching Hospitals NHS Trust, Stoke Mandeville and Wycombe General Hospitals, Thomas Addison Unit, St Georges Hospital, University Hospitals of Leicester NHS Trust, Warrington and Halton Hospitals, Watford General, St Albans City and Hemel Hempstead General Hospitals, Whittington Hospital

Update since publication

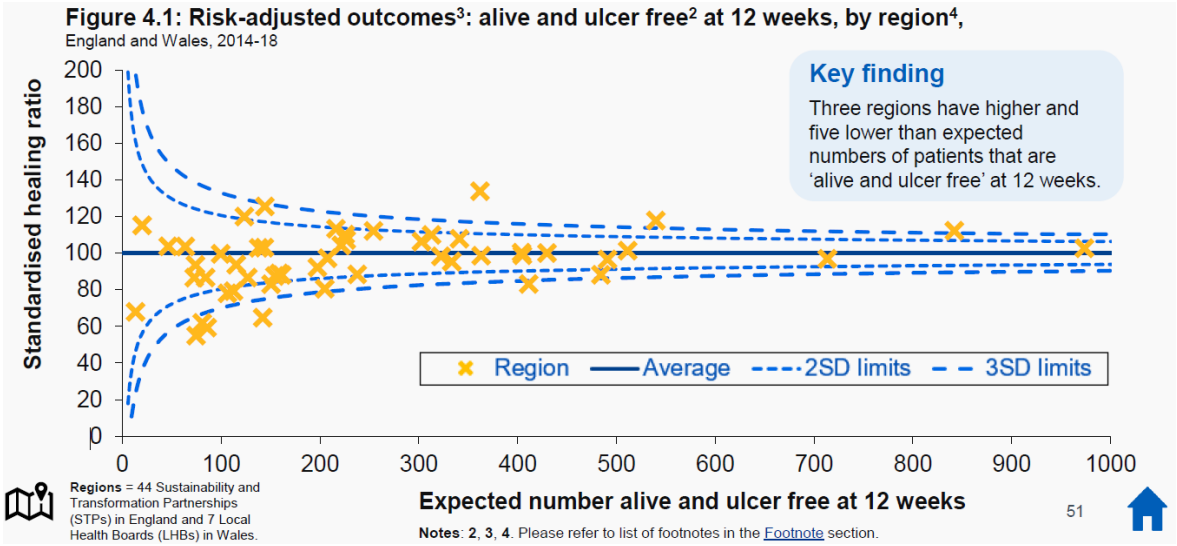
Since the publication of this work, the methodology and findings have been handed over to NHS Digital to inform the implantation of the National Diabetes Footcare Audit (NDFA). NDFA started collecting data in 2014 as an ongoing, rolling data collection of people presenting to multi-disciplinary foot teams with an incident diabetic foot ulcer [97]. It aims to collect data on the characteristics, clinical care and outcomes of all people presenting to multi-disciplinary foot care teas across England and Wales.

The latest report covers the period 1st April 2015 to 31st March 2018 and includes data on 33,155 new foot ulcer episodes in 27,700 people [98]. The findings of this larger cohort spanning a longer time period are similar to those found in the pilot study and presented above. Just under half (48.7%) of people were alive and ulcer free 12 weeks after initial presentation to the multi-disciplinary team. This compares to 49.4% in the pilot data collection. The organisational placement of the NDFA as managed by NHS Digital and part of the group of audits included in the National Diabetes Audit facilitates easy linkage to the core National Diabetes Audit data to include data on risk factors and intermediate diabetes outcomes. Regression models seeking to explain the chance of being alive and ulcer free 12 weeks after presentation indicated that ulcer characteristics (ischemia, area and depth) are the strongest predictors of this

outcome. Another notable finding was that duration of diagnosed diabetes is statistically significantly associated with being alive and ulcer free at 12 weeks after initial presentation but no such association exists with age at presentation with foot ulcer.

One of the key aims of the pilot and subsequently the NDFA was to identify a methodology for appropriately identifying variation in outcomes amongst those presenting with diabetic foot ulcers. The high level of co-morbidity amongst this group and the chronic nature of ulcers make crude outcomes rates a blunt measure. The approach taken in NDFA follows the methodology of the standardised healing ratio detailed above but expands the variables included in the case mix adjustment. This facilitates the identification of regions where outcomes are either statistically significantly better or worse than would be expected based on the characteristics of their population with diabetic foot disease (see **Figure 4.2** below).

Figure 4.2: Risk adjusted outcomes: alive and ulcer free at 12 weeks, taken from the National Diabetes Footcare Audit Fourth Annual Report



Chapter 5: Longitudinal cohort of people presenting with diabetic foot ulcers in northern England

Introduction

The role of hyperglycaemia in increasing the risk of peripheral vascular disease and neuropathy is well documented. This creates a physiological state in which the development and persistence of foot ulcers is increased and lifetime risk of an individual with diabetes developing a foot ulcer is estimated to be 25% [99]. This results in a considerable burden to the healthcare provider, with annual costs estimated to be £580 million per annum in England [100], and to the individual. There is a need to understand the morbidity and mortality of people presenting with diabetic foot ulcers using contemporary data 'real world' data on people with diabetic foot disease outside specific research trials. This population based study examines the characteristics and outcomes of people with incident diabetic foot ulcers in a longitudinal cohort of people presenting with diabetic foot ulcers in Salford in the north of England.

Methods

Since 2001 data on all people presenting to the multi-disciplinary foot care team with an incident diabetic foot ulcer in the city of Salford, England has been recorded in an electronic system as part of routine clinical practice. This recorded the patient's age, details of the presenting ulcer (the main site of the ulcer, whether cellulitis was present, whether the ulcer extended to the bone and whether there was evidence of peripheral vascular disease) and time to ulcer healing. A cohort of people presenting between 1st January 2001 and 31st December 2012 was identified. Records for these individuals have been linked to complementary primary and secondary care electronic health records using the unique National Health Service number to identify type of diabetes, cardiovascular risk factors (HbA1c, blood pressure, cholesterol, body mass index, kidney function as measured by eGFR, smoking status) and death registrations to June 2013.

An ulcer severity score (range 0 to 4) was created with one point being allocated for the ulcer being on the hind foot, cellulitis being present, the ulcer extending to the bone and having evidence of peripheral vascular disease. This is as close

an approximation of the SINBAD score [84] as possible considering the dataset collated.

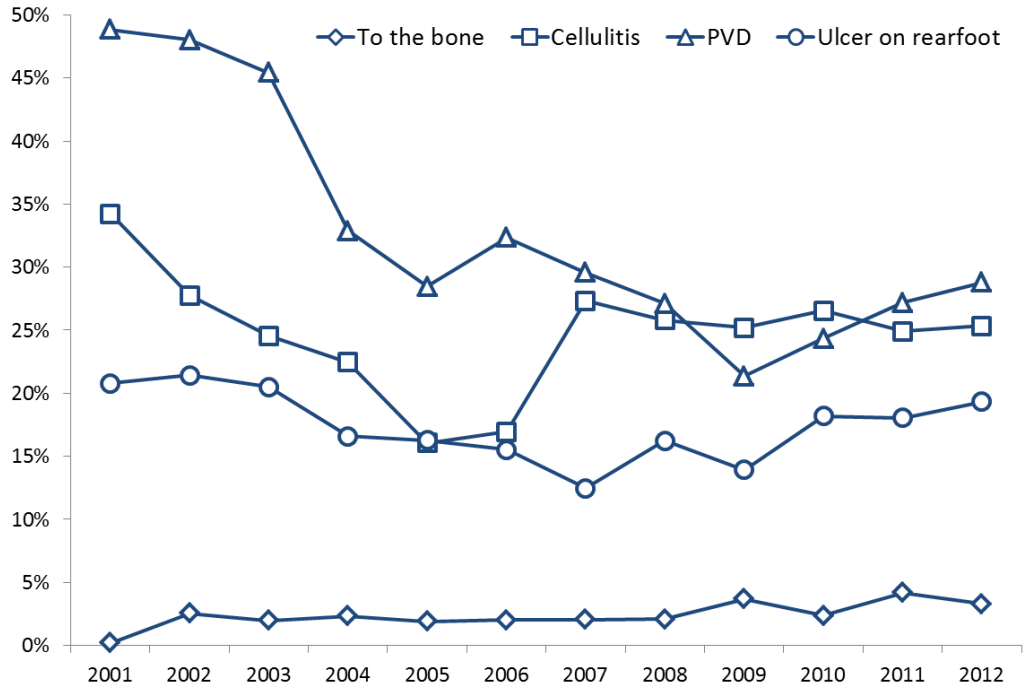
Statistical analysis

Changes over time in the mean age at presentation of incident foot ulcer and the mean ulcer severity score were assessed using one way ANOVA tests. Differences in the proportion of the cohort that were male and who had a previously healed ulcer were tested using chi-square statistics. Mortality rates standardised to the European Standard Population were calculated for one year and two years from initial presentation of a foot ulcer. Confidence intervals for standardised mortality rates were computed using the Exact method [101]. Logistic regression models were created to assess the predictive factors for the ulcer healing within 90 days of first presentation. Cox regression models were constructed to explore the relationship between patient characteristics, the nature of the presenting ulcer, known cardiovascular risk factors and survival.

Results

Between 2001 and 2012 there were 8028 incident cases of diabetic foot ulcers among 2937 people. There has been no change in age at presentation (mean 68.6 years, median 70 years) or the proportion of patients that were male (59.4%). 2.4% of incident ulcers were deep enough to involve the bone, 24.0% were accompanied by cellulitis and 32.7% were in people with peripheral vascular disease. The mean ulcer severity score fell from 1.04 in 2001 to 0.76 in 2012 ($p<0.005$). This was accompanied by a change in ulcer characteristics. The percentage of ulcers that were deep enough to reach the bone and were on the rear foot remained relatively constant over time whilst the proportion of people presenting with peripheral vascular disease fell from 48.8% in 2001 to 28.8% in 2012 ($p<0.005$). The proportion of people reporting a previously healed foot ulcer reduced from 67.2% in 2001 to 44.6% in 2012 ($p<0.005$).

Figure 5.1: Characteristics of ulcers over time

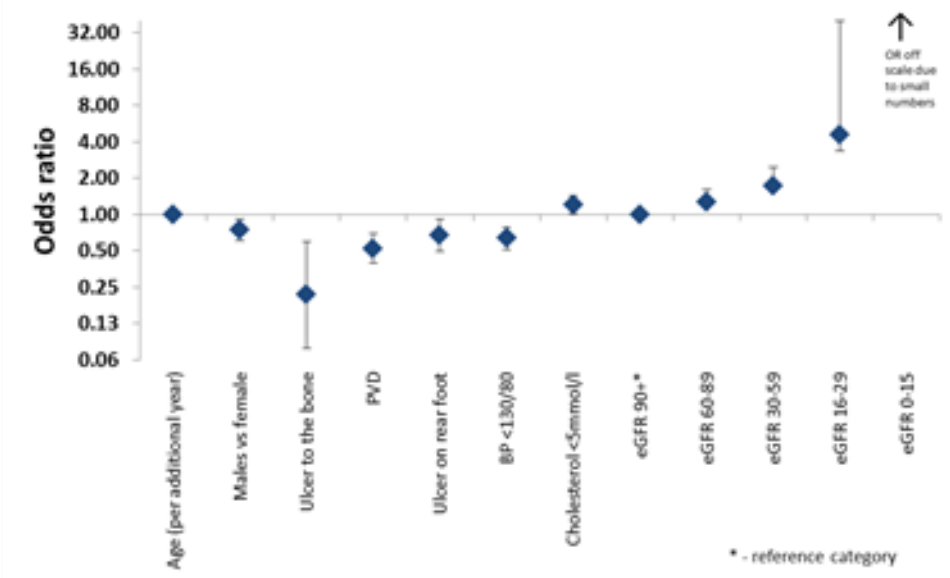


Median time to healing was 79 days (IQR 21-320 days) and 45.1% healed within 90 days. Men (OR 0.87 95% CI 0.77-0.98) and older people (OR 1.01 95% CI 1.00-1.01 per additional year) were less likely to heal within 90 days. Having peripheral vascular disease (OR 0.75, 95% CI 0.66-0.85), cellulitis (OR 0.84, 95% CI 0.74-0.96), an ulcer to the bone (OR 0.46, 95% CI 0.30-0.70) were significantly associated with a lower chance of the incident ulcer healing within 90 days whilst having a previously healed ulcer increased the chance of healing (OR 1.53, 95% CI 1.36-1.71).

The foot care records of 1728 (58.0%) individuals could be linked to their general health record to provide sufficient data for analysis. Age (OR 0.99 per additional year of age, 95% CI 0.98-0.99) and being male (OR 0.74 95% CI 0.60-0.92), increased depth (probing to bone) (OR 0.22 95% CI 0.08-0.60), rear foot location (OR 0.68 95% CI 0.49-0.92), peripheral vascular disease (OR 0.52 95% CI 0.39-0.69) and blood pressure below the current NICE recommended target for people with vascular disease (130/80) (OR 0.64 95% CI 0.51-0.79) were associated with a lower chance of healing in 90 days. Total cholesterol below 5mmol/l was linked with ulcer healing (OR 1.20 95% CI 1.01-1.41) in 90 days, whereas kidney function was inversely related to the chance of healing in 90 days (OR compared to eGFR 90+ for eGFR 60-89 1.27 95% CI 1.01-1.60, eGFR 30-59 1.71 95 CI 1.19-

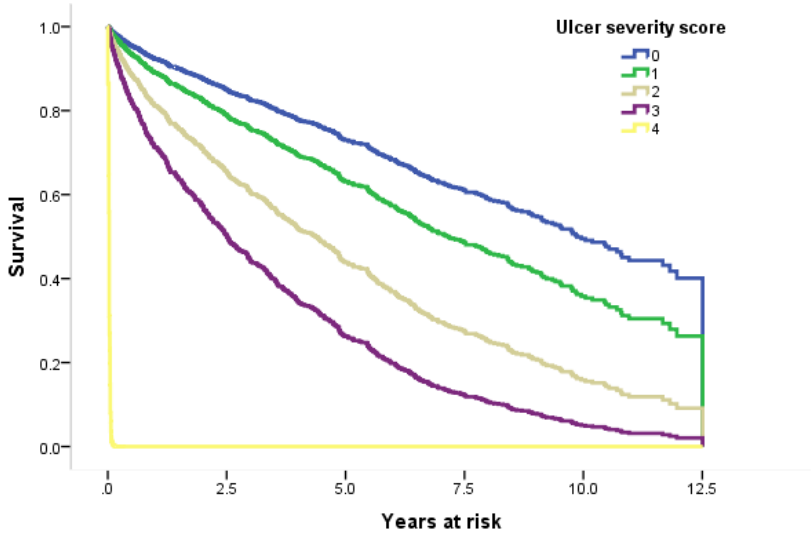
2.47, eGFR <30 4.57 95% 0.52-39.92) (see **Figure 5.1**). Cellulitis, type of diabetes, HbA1c, body mass index and smoking were not associated with ulcer healing rates at 90 days.

Figure 5.2: Odds ratios associated with ulcer healing within 90 days



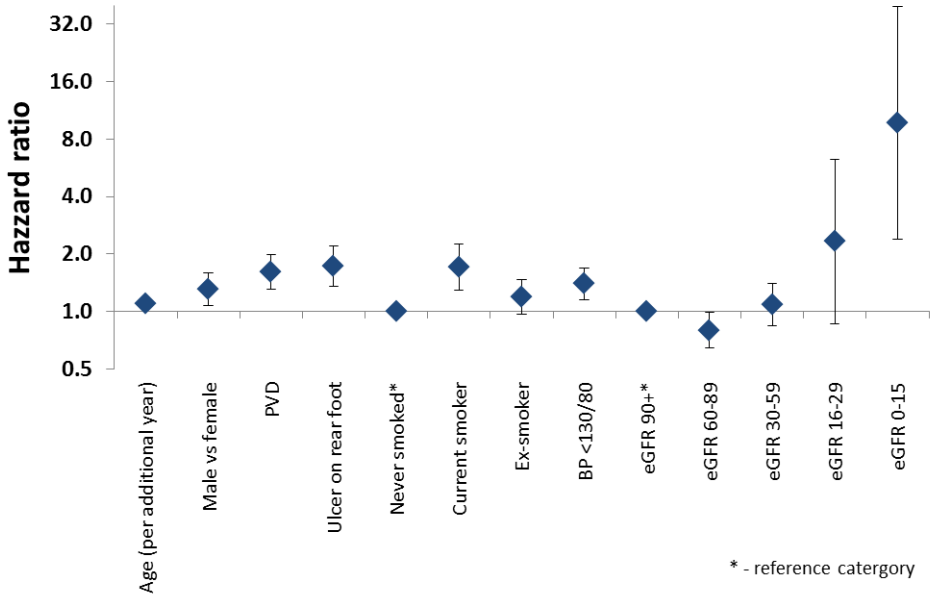
In this cohort crude mortality one year from initial presentation was 13.1% and 19.5% at two years. Age and sex standardisation to the European Standard Population adjusted one year mortality to 63.5 (95% CI 51.0-77.4) per 1000 person years for men and 47.3 (95% CI 38.9-56.6) per 1000 person years for women. Over the time period studied there was a non-statistically significant decline in morality. For those presenting with incident foot ulcers in the final three years of the data collection (2010 to 2012) one year standardised mortality rates were 52.2 (95% CI 35.1-74.0) per 1000 person years for males and 40.4 (23.7-62.8) per 1000 person years for females. This compares to 92.3 (95% CI 48.6-144.0) per 1000 person years and 59.7 (95%CI 44.9-77.4) per 1000 person years for men and women respectively between 2001 and 2003. A higher ulcer severity score was associated with shorter survival (see Figure 5.2).

Figure 5.3: Survival by ulcer severity score



Increasing age (HR 1.10 per additional year of age, 95% CI 1.09-1.11) and being male (HR 1.31 95% CI 1.08-1.60) were significantly associated with shorter survival. Peripheral vascular disease (HR 1.61 95% CI 1.30 - 1.99) and rear foot ulcers (HR 1.72 95% CI 1.35 - 2.20) were also significantly associated with shorter survival. Smokers had significantly higher mortality than those who had never smoked (HR 1.71 95% CI 1.30 – 2.25) whilst ex-smokers showed a non-significant raised risk of dying (HR 1.19 95% CI 0.97 - 1.47). Blood pressure below 130/80 was associated with higher mortality (HR 1.39 95% CI 1.15 - 1.69). Poor kidney function was associated with higher mortality but only reached statistical significance with very advanced disease (eGFR<15 (OR 9.71 95% 2.38-39.64) (see **Figure 5.3**). The depth of the incident ulcer and cellulitis, type of diabetes, HbA1c, body mass index and lipid profile were not significantly associated with differential mortality.

Figure 5.4: Hazard ratios associated with risk of dying



Discussion

This analysis represents a contemporary study examining the characteristics and outcomes of people presenting with diabetic foot ulcers. It uses data that was routinely collated as part of clinical practice to chart the change in characteristics of people presenting with diabetic foot ulcers in Salford since 2001. There have been several studies that have documented the decline in lower limb amputations among people with diabetes over a similar time period [24]. Whilst the occurrence of lower limb amputations is often used as a measure of outcome when considering foot health in people with diabetes, surgery (whether resulting in amputation or not) is a treatment rather than a patient centred outcome and subject to variation in surgical practice and culture that cannot be fully explained by differences in presenting patients [79,102]. Assessing ulcer healing and mortality provides a more holistic picture of outcomes for the cohort studied.

In this cohort just under half of ulcers healed within 12 weeks. This is similar to the ulcer healing rate of 49.4% within 90 days reported in the pilot study collating data from 23 multi-disciplinary foot care teams across England [103]. It is also similar to the proportion of people reported to be alive and ulcer free 12

weeks after initial presentation (48.2%) in the 22,653 cases analysed in the most recent National Diabetes Footcare Audit for England and Wales [104].

Whilst the demographic characteristics of those presenting with diabetic foot ulcers has not changed over the time period studied, the overall severity of the ulcers at presentation to a multi-disciplinary foot team is lower. One possible explanation for this is a growing understanding amongst people with diabetes and non-foot specialist health professionals of the importance of early identification of foot ulcers and prompt referral to multi-disciplinary foot care teams. The clear decline in the number of ulcers where peripheral vascular disease is present suggests that the general aim of reducing cardiovascular risk in people with diabetes has altered the characteristics of foot ulcers at presentation.

The short term mortality of people presenting with diabetic foot disease was high with almost one in five dying in the following two years. This death rate is partly a reflection of the age of people with incident diabetic foot ulcers and is comparable with a study of 185 people with incident diabetic foot ulcers presenting in Liverpool between 1994 and 1998 which reported 19.5% mortality after two years and 44% after five years [105]. A larger, more recent analysis of 20,737 people developing a diabetic foot ulcer reported a similar five year mortality risk (42%) [106]. However, given the average age of people presenting with diabetic foot ulcers high crude mortality rates are to be expected and age standardisation is needed to make meaningful comparisons. After age standardisation one year mortality in this cohort of people with diabetic foot ulcers in Salford was still high at 51.5 and 41.7 deaths per 1000 person years for males and females respectively for the period 2010 to 2012. This is similar to 41.5 per 1000 person years in a cohort resident in Cheshire, England who were followed up from 2004 to 2015 [106]. Comparisons between the mortality experienced by those presenting with diabetic foot ulcers and the general population are stark. One year mortality rates of 8.1 deaths per 1000 person years for men and 5.7 deaths per 1000 person years for women in the general population of Salford over the same three years (2010-2012) [107] meaning that people presenting with diabetic foot ulcers are approximately seven times more likely to die in the twelve months following presentation to the multi-

disciplinary foot care team than their local peers in the general population. They also have approximately five times the risk of death for all people with diagnosed diabetes living in Salford [55]. These findings of increased risk of dying illustrate the poor outcomes faced by people at the time of presentation with a diabetic foot ulcer.

In this cohort having an ulcer on the hind foot, peripheral vascular disease, smoking (either currently or in the past) and poor kidney function were associated with a greater risk of dying. Similar risk factors (peripheral ischaemia, ulcer size and depth and the presence of neuropathy) for not being alive and ulcer free 12 weeks after initial presentation have been identified by the National Diabetes Footcare Audit [104]. Further insight into mortality risk amongst people with diabetic foot ulcers would be gleaned by considering the cause of death and potential interactions between the ulcer and pre-existing co-morbidities.

This data provides a comprehensive picture of the characteristics and outcomes of people presenting with diabetic foot ulcers in Salford over a ten year period. However, this data is limited to a specific geographical area covered by a particular health service. Previous work has shown that amputations among people with diabetes are more common amongst people living in deprived areas [108]. Salford is an area with higher than average social deprivation ranking 42nd and 26th out of 327 local authorities in England for income deprivation and wider deprivation encompassing education, health and living environment respectively [109]. It is therefore likely that the incidence and severity of foot ulcers in Salford is higher than would be expected compared to national figures. Nonetheless, this analysis provides insight that may be applicable across England and beyond. It shows high levels of morbidity and mortality among people presenting with diabetic foot ulcers. Given the clear association between indicators of poor vascular, renal health and mortality, measures to improve outcomes amongst those with diabetic foot ulcers may need to focus on longer term prevention of macro and micro vascular damage. This is likely to require input from across the range of professionals and clinical settings providing care for people with diabetes and results will be seen over the medium to long term.

Update

In the period since this chapter was produced the National Diabetes Footcare Audit has been established and matured to provide meaningful data on the characteristics, care and short term outcomes of people with diabetic foot ulcers (see previous chapter). A similar study of people presenting with diabetic foot ulcers between 2003 and 2017 to South Devon community podiatry service and Torbay Hospital Multi-Disciplinary Foot Team has been published [110]. In line with the analysis in this thesis, it reports that there has not been a change in the age or sex of people presenting with diabetic foot ulcers but the proportion where peripheral vascular disease is evident has declined. It is worth noting that the mean age of presentation in this cohort (76.2 years old between 2013-17 compared to 68.6 years in Salford). This may be a reflection of the higher level of social deprivation in Salford compared to South Devon and the association between social deprivation and a greater risk of developing foot disease and at younger ages. It also found high absolute mortality rates with 10 year survival of 69.8% among those aged less than 65 years old rising to 5.1% in those aged 81 or older at first presentation. Given the higher mean age at presentation in this study greater absolute mortality is to be expected and full adjustment for age, comorbidity and ulcer characteristics would be needed to provide a more meaningful comparison.

Chapter 6: Association between routine care processes completion and mortality in people with diabetes: Analysis of data from the National Diabetes Audit for England

Introduction

There is robust evidence that blood glucose control, blood pressure control reduce both the microvascular and macrovascular complications of diabetes, with blood lipid control lowering macrovascular outcomes [111–113]. Accordingly treatment target goals for glycaemic control as measured by HbA1c levels, for blood pressure and for lipid levels are at the centre of every national and international diabetes care guideline [43,114,115].

In order to know whether these treatment targets have been reached and to review treatment they need to be measured. Their measurement, along with review of weight and smoking behaviour plus surveillance for early detection of complications (kidney disease, foot and eye), have in the United Kingdom been called the core nine diabetes care processes. The National Institute for Health and Clinical Excellence recommends that people with Type 1 [42] and Type 2 [43] diabetes are offered these nine care processes annually (measurement of HbA1c, blood pressure, cholesterol, body mass index, creatinine and urinary albumin, digital retinal examination, foot examination for sensory and circulatory impairment, and recording of smoking status).

While most international and national diabetes guidelines stress the importance of measuring these care processes the level of evidence to support this recommendation is usually not stated or, when it is, rated at the lowest standard of evidence i.e. that of “expert consensus” or “clinical experience” [115]. This reflects the fact that little has been published about whether or not care process completion *is itself* (causally) related to any of the final outcomes of diabetes such as micro and macro vascular complications and mortality or whether it is just a vehicle to support treatment target achievement.

In England and Wales, the National Diabetes Audit (NDA) has, every year since 2004, collected information from general and specialist electronic records on the rates of achievement of these care processes by provider organisation and published this information annually. Using routinely recorded patient level data from the NDA this analysis aims to assess whether the specific healthcare

activity of annual care processes completion is associated with the most final diabetes outcome, mortality.

Methods

The National Diabetes Audit extracts and combines electronic patient record data on people with diagnosed diabetes from primary and secondary care services annually. This routinely recorded data is collated to create a database of patient demographic characteristics (age, sex, ethnic group, social deprivation, type and duration of diabetes) and the annual occurrence and outcome of care processes (HbA1c, blood pressure, total cholesterol, creatinine, urinary albumin, body mass index, smoking status, foot examination and eye examination). During the period studied it did not include any medication data.

A cohort was identified of people with Type 1 or Type 2 diabetes registered with an English health provider, and included in all three of the National Diabetes Audit collections for the periods January 2008 to March 2009, January 2009 to March 2010 and January 2010 to March 2011 and still alive on 1st April 2011. Individuals without valid age or sex records were excluded from the analysis. Type of diabetes was identified as that most recently recorded. The mean number of care processes received per year across these three data collection periods was calculated for each individual. An individual was classified as receiving a care process if it had been recorded as being undertaken within the specified periods irrespective of the result obtained or recorded. Mean values for HbA1c, systolic blood pressure, diastolic blood pressure, total cholesterol and body mass index were calculated for the same three-year period. The cohort was matched to Office for National Statistics death registrations to identify mortality up to 31st December 2015. Deaths were classified as having a primary cause of cardiovascular disease (ICD-10 codes I01-I99) and non-cardiovascular disease (all ICD-10 codes except I01-I99). Home postcodes were used to link to the Indices of Multiple Deprivation [109] to derive an area based measure of social deprivation.

Statistical analysis

Cox regression models were created to investigate the association between mortality and the average number of care processes received after adjusting for

- Age and sex
- Age, sex, ethnic group, social deprivation and smoking status
- Age, sex, ethnic group, social deprivation, smoking status, HbA1c, systolic blood pressure, diastolic blood pressure, total cholesterol and body mass index

All variables except age were analysed as categorical variables to allow the non-linear associations between risk factors and mortality to be included in the models. An additional category of 'missing data' was also included for each variable except age and sex to take account of the fact that people who had not received a care process would not have a valid measurement of the outcome or risk factor.

Separate models were calculated for deaths due to cardiovascular disease and those due to non-cardiovascular disease. To investigate whether the relationship between care processes and mortality varied by ethnic group separate models were produced for people from white ethnic groups (White British, White Irish and White 'other' groups), from south Asian ethnic groups (Indian, Pakistani and Bangladeshi) and from Black ethnic groups (Black African and Black Caribbean). Given its importance to future risk of mortality, models were also created for individuals stratified into quintiles based on social deprivation.

Results

A total of 215,101 people with Type 1 diabetes and 2,182,409 people with Type 2 diabetes were identified within the three data collections. 534 (0.2%) people with Type 1 diabetes and 4269 (0.2%) people with Type 2 diabetes were excluded due to a lack of a valid age or sex recorded. Over the follow up period there were 22,084 deaths (10.3%) amongst those with Type 1 diabetes and 463,365 (21.2%) deaths in those with Type 2 diabetes.

After adjusting for age and sex, completing less than five care processes per year compared to completing all nine care processes was associated with a higher risk of dying from all causes (Hazard ratio (HR) 2.22 (95% CI 2.12-2.32) for those with Type 1 diabetes and 2.16 (95% CI 2.14-2.18) for those with Type 2 diabetes) (see **Table 6.1 and Figures 6.1a. 6.1b**). The additional risk of mortality reduces as the mean number of care processes completed increases for people with both Type 1 and Type 2 diabetes. Adjusting for demographic characteristics (age, sex, ethnic group, deprivation and smoking status) and cardiovascular risk factors (HbA1c, blood pressure, total cholesterol and body mass index) attenuated the hazard ratio associated with a mean of less than five care processes per year to 1.71 (95% CI 1.62-1.82) for those with Type 1 diabetes and to 1.71 (95% CI 1.68-1.73) for those with Type 2 diabetes.

Table 6.1: Hazard ratios for mortality from all causes associated with mean number of care processes received per year by type of diabetes

		Type 1 diabetes	Type 2 diabetes
Number included in analysis		214,567	2,182,409
Number of events (deaths)		22,084	463,365
Adjusted for age and sex	<5	2.22 (2.12-2.32)	2.16 (2.14-2.18)
	5-5.9	1.87 (1.76-1.98)	1.84 (1.81-1.86)
	6-6.9	1.73 (1.64-1.82)	1.61 (1.6-1.63)
	7-7.9	1.36 (1.3-1.42)	1.34 (1.33-1.35)
	8-8.9	1.05 (1.01-1.1)	1.06 (1.05-1.07)
	9	Reference group	Reference group
Adjusted for age, sex, ethnic group, deprivation and smoking status	<5	2.26 (2.16-2.37)	2.09 (2.07-2.12)
	5-5.9	1.85 (1.74-1.96)	1.84 (1.82-1.87)
	6-6.9	1.74 (1.65-1.83)	1.63 (1.61-1.65)
	7-7.9	1.37 (1.31-1.43)	1.35 (1.34-1.36)
	8-8.9	1.08 (1.03-1.12)	1.07 (1.06-1.07)
	9	Reference group	Reference group
Adjusted for age, sex, ethnic group, deprivation, smoking status, HbA1c, blood pressure, total cholesterol and body mass index	<5	1.71 (1.62-1.82)	1.71 (1.68-1.73)
	5-5.9	1.56 (1.47-1.66)	1.6 (1.58-1.63)
	6-6.9	1.56 (1.48-1.64)	1.49 (1.47-1.5)
	7-7.9	1.29 (1.23-1.35)	1.29 (1.27-1.3)
	8-8.9	1.05 (1.01-1.1)	1.05 (1.05-1.06)
	9	Reference group	Reference group

Figure 6.1a: Hazard ratios for mortality from all causes associated with mean number of care processes received per year, Type 1 diabetes

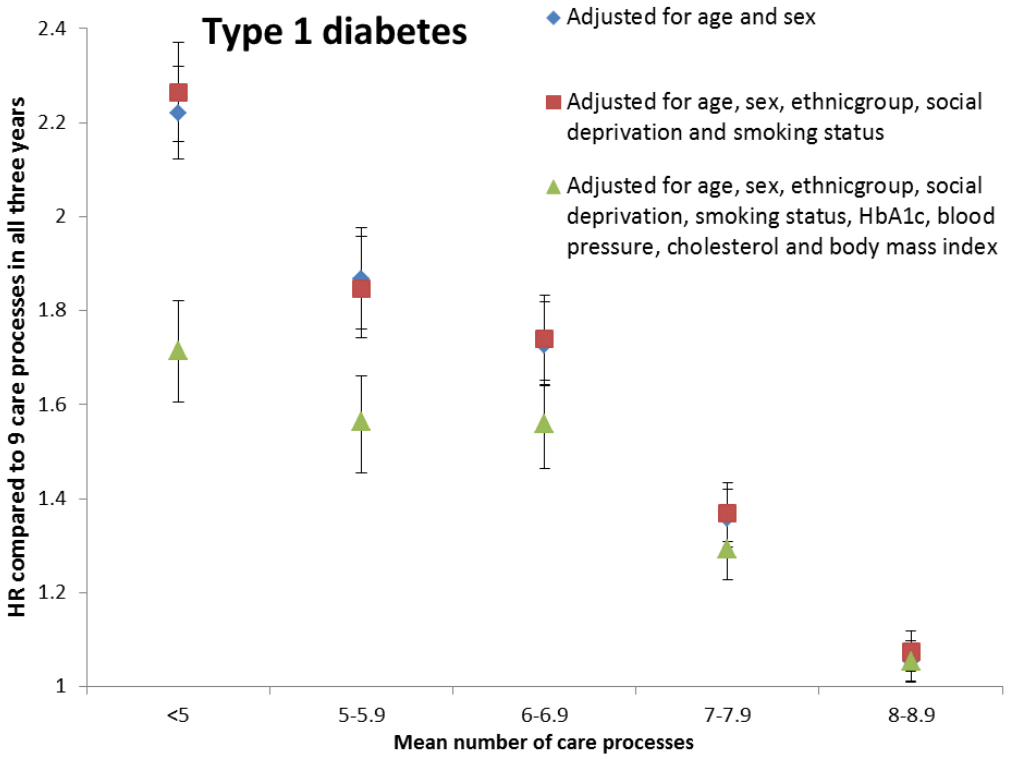
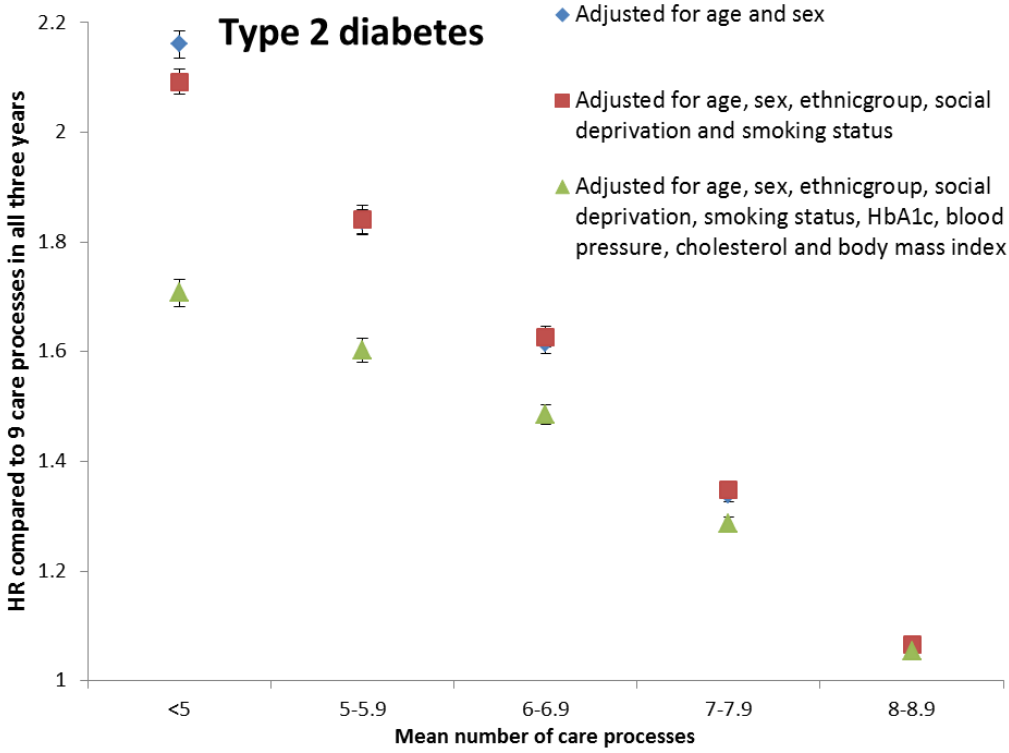


Figure 6.1b: Hazard ratios for mortality from all causes associated with mean number of care processes received per year, Type 2 diabetes



Associations between missing data and mortality varied across the variables used to adjust for confounding in the survival models. Not having a valid home postcode recorded (and therefore missing data on social deprivation) was associated with the highest hazard ratios for death (HR 3.15 95% CI 1.92-5.14 for Type 1 diabetes and 2.31 95% CI 2.08-2.56 for Type 2 diabetes) (**see Table 6.2**). Missing data on ethnic group, body mass index and total cholesterol were also associated with higher risks of mortality for people with Type 1 and Type 2 diabetes.

Table 6.2: Hazard ratios for mortality from all causes by type of diabetes

		Type 1 diabetes	Type 2 diabetes
n (deaths)		214,567 (22,084)	2,182,409 (463,365)
Age (per additional year)		1.08 (1.08-1.08)	1.09 (1.08-1.09)
Male		1.22 (1.18-1.25)	1.19 (1.18-1.19)
Social deprivation	Most deprived	1.56 (1.49-1.63)	1.3 (1.29-1.31)
	2nd most deprived	1.37 (1.32-1.44)	1.18 (1.17-1.19)
	3rd most deprived	1.2 (1.15-1.26)	1.11 (1.1-1.12)
	2nd least deprived	1.12 (1.07-1.17)	1.05 (1.04-1.07)
	Least deprived	Reference group	Reference group
	Missing data	3.15 (1.92-5.14)	2.31 (2.08-2.56)
Ethnic group	White	Reference group	Reference group
	Mixed	0.95 (0.81-1.12)	0.68 (0.65-0.71)
	South Asian	0.86 (0.79-0.93)	0.66 (0.65-0.67)
	Black	0.72 (0.65-0.78)	0.6 (0.59-0.62)
	Other	0.98 (0.9-1.08)	0.85 (0.84-0.87)
	Missing data	1.28 (1.23-1.32)	1.31 (1.3-1.32)
Smoking status	Current smoker	1.7 (1.64-1.76)	1.72 (1.71-1.74)
	Previous smoker	1.16 (1.12-1.2)	1.2 (1.19-1.21)
	Non-smoker, unknown history	1.28 (1.23-1.34)	1.37 (1.35-1.38)
	Never smoked	Reference group	Reference group
	Missing data	0.93 (0.85-1.01)	1.38 (1.35-1.4)
HbA1c (mmol/mol)	<48	1.26 (1.19-1.34)	1.07 (1.06-1.08)
	48-52	1.05 (0.98-1.12)	0.95 (0.94-0.96)
	53-57	Reference group	Reference group
	58-63	0.99 (0.94-1.05)	1.09 (1.07-1.1)
	64-68	1 (0.94-1.06)	1.18 (1.16-1.2)
	69-74	1.04 (0.98-1.1)	1.28 (1.26-1.3)
	75-79	1.17 (1.1-1.25)	1.32 (1.29-1.34)
	80+	1.54 (1.46-1.62)	1.56 (1.54-1.58)
	Missing data	1.17 (1.08-1.28)	0.91 (0.9-0.93)
Systolic blood pressure (mmHg)	<100	1.3 (1.24-1.36)	1.45 (1.44-1.47)
	100-119	1.08 (1.03-1.12)	1.13 (1.12-1.13)
	120-139	Reference group	Reference group

	140-159	1.04 (0.99-1.08)	1.01 (1-1.02)
	160-179	1.18 (1.12-1.25)	1.09 (1.08-1.11)
	180+	1.47 (1.38-1.57)	1.25 (1.23-1.27)
	Missing data	0.59 (0.33-1.05)	1.44 (1.22-1.69)
Diastolic blood pressure (mmHg)	<70	1.05 (1-1.09)	1.16 (1.15-1.18)
	70-79	0.93 (0.89-0.97)	1.02 (1.01-1.02)
	80-89	Reference group	Reference group
	90-99	1.13 (1.04-1.24)	1.05 (1.03-1.07)
	100+	1.53 (1.3-1.81)	1.21 (1.16-1.26)
	Missing data	1.31 (0.74-2.34)	0.63 (0.54-0.75)
Total cholesterol	<4mmol/l	Reference group	Reference group
	4-4.9mmol/l	0.83 (0.81-0.86)	0.89 (0.88-0.89)
	5+mmol/l	0.93 (0.9-0.97)	0.88 (0.87-0.88)
	Missing data	1.1 (1.03-1.18)	1.14 (1.12-1.16)
Body mass index (kg/m^2)	<18.5	2.62 (2.4-2.86)	2.01 (1.96-2.06)
	18.5-24.9	1.25 (1.21-1.3)	1.27 (1.26-1.28)
	25-29.9	Reference group	Reference group
	30-34.9	1.14 (1.09-1.18)	1 (0.99-1.01)
	35-39.9	1.4 (1.33-1.49)	1.11 (1.1-1.12)
	40+	1.83 (1.71-1.97)	1.48 (1.46-1.5)
	Missing data	1.62 (1.53-1.72)	1.53 (1.51-1.55)
Mean care processes received	<5	1.71 (1.62-1.82)	1.71 (1.68-1.73)
	5-5.9	1.56 (1.47-1.66)	1.6 (1.58-1.63)
	6-6.9	1.56 (1.48-1.64)	1.49 (1.47-1.5)
	7-7.9	1.29 (1.23-1.35)	1.29 (1.27-1.3)
	8-8.9	1.05 (1.01-1.1)	1.05 (1.05-1.06)
	9	Reference group	Reference group

Amongst people with Type 1 diabetes the association between less than five care processes and additional risk of death was lower for death due to cardiovascular disease than for deaths from all other causes (HR 1.50 95% CI 1.36-1.67 compared to 1.83 95% CI 1.70-1.97) (see **Table 6.3**). A similar pattern was found in people with Type 2 diabetes where the hazard ratio associated with a mean of less than five care processes per year is 1.61 (95% CI 1.57-1.65) for deaths with a primary cause of cardiovascular disease and 1.76 (95% CI 1.73-1.79) for death with a primary cause of non-cardiovascular disease.

Table 6.3: Hazard ratios for mortality from all causes associated with mean number of care processes received per year by type of diabetes and primary cause of death

Mean care processes		Type 1 diabetes	Type 2 diabetes
Cardiovascular disease	<5	1.50 (1.36-1.67)	1.61 (1.57-1.65)
	5-5.9	1.51 (1.36-1.67)	1.52 (1.48-1.56)
	6-6.9	1.47 (1.34-1.6)	1.42 (1.39-1.45)
	7-7.9	1.25 (1.16-1.35)	1.26 (1.24-1.28)
	8-8.9	1.02 (0.96-1.09)	1.05 (1.04-1.07)
	9	Reference group	Reference group
Non-cardiovascular disease	<5	1.83 (1.7-1.97)	1.76 (1.73-1.79)
	5-5.9	1.6 (1.48-1.72)	1.65 (1.62-1.68)
	6-6.9	1.61 (1.51-1.72)	1.52 (1.5-1.54)
	7-7.9	1.32 (1.25-1.4)	1.3 (1.28-1.31)
	8-8.9	1.07 (1.02-1.13)	1.05 (1.05-1.06)
	9	Reference group	Reference group

After adjustment for age, sex, social deprivation, ethnic group, smoking status, HbA1c, systolic and diastolic blood pressure, cholesterol and body mass index.

The additional risk of dying associated with fewer achieved care processes was higher among people living in more deprived neighbourhoods compared to their peers in less deprived areas (see **Table 6.4**).

Table 6.4: Hazard ratios for mortality from all causes associated with mean number of care processes received per year by type of diabetes and deprivation quintile

Mean number of care processes		Type 1 diabetes	Type 2 diabetes
Least deprived	<5	1.58 (1.4-1.79)	1.62 (1.58-1.67)
	5-5.9	1.45 (1.29-1.64)	1.59 (1.55-1.64)
	6-6.9	1.55 (1.39-1.73)	1.52 (1.49-1.56)
	7-7.9	1.28 (1.16-1.41)	1.31 (1.29-1.34)
	8-8.9	1.12 (1.02-1.22)	1.07 (1.05-1.09)
	9	Reference group	Reference group
2nd least deprived	<5	1.39 (1.23-1.59)	1.61 (1.56-1.67)
	5-5.9	1.46 (1.29-1.66)	1.58 (1.53-1.63)
	6-6.9	1.44 (1.28-1.61)	1.45 (1.41-1.49)
	7-7.9	1.3 (1.18-1.43)	1.31 (1.28-1.33)
	8-8.9	1.08 (0.99-1.18)	1.05 (1.03-1.06)
	9	Reference group	Reference group
3rd most deprived	<5	1.91 (1.67-2.17)	1.67 (1.62-1.73)
	5-5.9	1.77 (1.55-2.02)	1.56 (1.51-1.61)
	6-6.9	1.59 (1.42-1.78)	1.48 (1.44-1.52)
	7-7.9	1.25 (1.13-1.38)	1.28 (1.25-1.31)
	8-8.9	0.98 (0.9-1.07)	1.05 (1.03-1.07)
	9	Reference group	Reference group
2nd most deprived	<5	1.94 (1.68-2.23)	1.85 (1.78-1.91)
	5-5.9	1.65 (1.43-1.89)	1.66 (1.61-1.72)
	6-6.9	1.66 (1.48-1.87)	1.49 (1.45-1.53)
	7-7.9	1.37 (1.24-1.52)	1.27 (1.24-1.3)
	8-8.9	1.03 (0.94-1.13)	1.04 (1.03-1.06)
	9	Reference group	Reference group
Most deprived	<5	2.08 (1.79-2.42)	1.89 (1.82-1.96)
	5-5.9	1.65 (1.41-1.92)	1.66 (1.6-1.72)
	6-6.9	1.64 (1.43-1.88)	1.49 (1.44-1.53)
	7-7.9	1.3 (1.16-1.46)	1.25 (1.22-1.28)
	8-8.9	1.09 (0.98-1.2)	1.06 (1.04-1.08)
	9	Reference group	Reference group

After adjustment for age, sex, ethnic group, smoking status, HbA1c, systolic and diastolic blood pressure, cholesterol and body mass index.

In the most deprived fifth of neighbourhoods the fully adjusted hazard ratio associated with a mean of less than five care processes was 2.08 (95% CI 1.79-2.42) for those with Type 1 diabetes and 1.89 (95% CI 1.82-1.96) for those with Type 2 diabetes. By comparison the equivalent hazard ratios for people living in the least deprived areas are 1.58 (95% CI 1.40-1.79) for Type 1 diabetes and 1.62 (95% CI 1.58-1.67) for Type 2 diabetes.

There were also statistically significant differences by ethnic group. For each ethnic group fewer achieved care processes were associated with an increased risk of mortality (see **Table 6.5**).

Table 6.5: Hazard ratios for mortality from all causes associated with mean number of care processes received per year by type of diabetes and ethnic group

Mean number of care processes		Type 1 diabetes	Type 2 diabetes
White ethnic groups	<5	1.82 (1.69-1.95)	1.87 (1.83-1.9)
	5-5.9	1.62 (1.51-1.74)	1.65 (1.62-1.68)
	6-6.9	1.6 (1.5-1.7)	1.53 (1.51-1.55)
	7-7.9	1.32 (1.25-1.39)	1.33 (1.32-1.35)
	8-8.9	1.08 (1.03-1.13)	1.08 (1.07-1.09)
	9	Reference group	Reference group
South Asian ethnic groups	<5	1.1 (0.77-1.58)	1.13 (1.06-1.22)
	5-5.9	1.5 (1.06-2.1)	1.24 (1.16-1.33)
	6-6.9	0.94 (0.67-1.33)	1.26 (1.19-1.34)
	7-7.9	0.91 (0.69-1.21)	1.15 (1.1-1.21)
	8-8.9	0.79 (0.63-1)	1 (0.96-1.04)
	9	Reference group	Reference group
Black ethnic groups	<5	1.32 (0.85-2.04)	1.42 (1.29-1.56)
	5-5.9	1.65 (1.11-2.46)	1.65 (1.51-1.82)
	6-6.9	1.76 (1.22-2.54)	1.37 (1.26-1.49)
	7-7.9	1.88 (1.38-2.56)	1.31 (1.22-1.41)
	8-8.9	1.19 (0.89-1.6)	1.09 (1.03-1.15)
	9	Reference group	Reference group

After adjustment for age, sex, social deprivation, smoking status, HbA1c, systolic and diastolic blood pressure, cholesterol and body mass index.

However, for people from White ethnic groups a mean of less than five care processes per year was associated with a greater additional risk of dying (HR 1.82 95% CI 1.69-1.95 for Type 1 diabetes, 1.87 95% CI 1.83-1.90 for Type 2 diabetes) than for those from south Asian ethnic groups (HR 1.10 95% CI 0.77-1.58 for Type 1 diabetes, HR 1.13 95% CI 1.06-1.22 for Type 2 diabetes) or from Black ethnic groups (HR 1.32 95% CI 0.85-2.04 for Type 1 diabetes, HR 1.42 95% CI 1.29-1.56 for Type 2 diabetes).

Discussion

In this large cohort of people with Type 1 and Type 2 diabetes individuals with a low number of achieved annual care processes had higher medium term mortality compared to those in whom all nine NICE recommended annual care processes were completed. People who received fewer annual care processes had a higher risk of dying over the medium term. However, after adjusting for treatment related factors known to increase complications risk (HbA1c, blood pressure, cholesterol and body mass index) and for missing data associated with not receiving care processes the additional risk of mortality, although attenuated, remained statistically and clinically significant. This suggests that the basic interactions with healthcare providers required to deliver the care processes in some way confer important health benefit over and above their role in identification and management of cardiovascular risk factors. In fact, the association between receiving fewer care processes and higher mortality was stronger for deaths due to non-cardiovascular disease than for cardiovascular disease further implying that these healthcare provider interactions may have positive benefits beyond better cardiovascular risk management. Of course, it may also be that independent of measured risk factors patients more engaged with self-care and lower risk lifestyles attend clinics more often and/or are more likely to request the specified care processes on a regular basis. A third possible factor is reverse causality, whereby people who do not feel well enough because of illness or subclinical illnesses, don't have the energy to attend all their appointments.

There are remarkable similarities between people with Type 1 and Type 2 diabetes in the direction and scale of the associations identified. In England

most people with Type 1 diabetes have specialist led care while for Type 2 diabetes the majority of people are managed in a primary care setting. So the association seems to be independent of type of diabetes and location of care. This would support the idea that it is the intensity of the interaction between people with diabetes and their care teams that must in some way influence, or mark, the risk of death. In turn this could be mediated by differences in the organisation of care or simply the opportunities for health care professionals and people with diabetes to meet, or else it points towards patient characteristics (whether more motivated at one end, or less motivated, frailer or with illness at the other end) that both lead to less care processes being achieved and at the same time to higher risks for CVD or non-CVD deaths.

The association appeared greatest amongst those living in more deprived neighbourhoods. Could this suggest that regular patient – healthcare interactions compensate for poorer self-efficacy or social support? The even greater risk seen in people with no recorded postcode might possibly be due to high representation in this group of people who are homeless or in transit accommodation such as asylum seekers. Lack of valid data on ethnic group was also associated with higher mortality but poor data on cardiovascular risk was not consistently linked to the risk of dying. This points to well organised and structured health care services potentially providing a more proactive, rather than reactive, approach to disease management.

The relationship between receipt of care processes and mortality also varies by ethnic group, but perhaps not in a manner expected. The additional risk of death amongst those receiving fewest annual care processes was approximately 80% for a person with Type 2 diabetes with White ethnicity compared to approximately 20% for someone with Type 2 diabetes who was of South Asian ethnicity. This may be due to the fact that the association between diabetes, hyperglycaemia and mortality varies across ethnic groups. A recent contemporary study using the CPRD cohort reported that the additional risk of dying attributable to diagnosed diabetes was actually lower in people from south Asian ethnic groups than in those from White ethnic groups [116]. This is despite a greater diagnosed incidence of cardiovascular disease amongst people from South Asian ethnic groups [117,118]. Thus all-cause mortality has been shown to

be lower than in people from White ethnic groups even after adjustment for socio-economic status and area of residence [119]. So perhaps this alignment of the size of the interaction effect with known ethnic differences in the additional risk of death associated with diabetes was to be expected.

Of course, these observational data cannot prove a causal relationship. So, as discussed above, the findings could be due to such factors as: accessibility and organisation of services; the beneficial effect of more frequent unstructured health conversations; or the frequency of organised care planning consultations. Equally, it is possible that they are confounded: by associations between poor attendance and hazardous behaviours; or an association between poor attendances and the prevalence or severity of co-morbidities. What can be confidently deduced, however, is that non-attenders for routine diabetes review are a group at high risk of mortality over the medium term. It may be that making efforts specifically to engage this group would yield worthwhile health benefits. Funders now recognise a need to study such groups more.

The principle strengths of this study are the size of the cohort included in the analysis and the fact that it is drawn comprehensively from real world healthcare records. The explicit treatment of missing data is also a strength. The suggestion that healthcare interactions are of themselves beneficial would have been enhanced if the dataset had been able to exclude the possibility that certain medications were used more often in frequent attenders or that co-morbidities were not over-represented in those having fewer care checks.

This work is the first analysis to consider the association between healthcare interactions (the receipt of annual care processes) and medium term health outcomes. So while new and tantalising these observations cannot do more than document an association. However, as the association persists even when a number of potential confounders are taken into account it implies that the organisation of routine care or the personal interactions between health care professionals and patients may have an independent and important influence on the excess risk of death among people with Type 1 and Type 2 diabetes. Further studies are required to corroborate and extend our findings.

Update

A recent literature review has not identified any further published studies on the association between the receipt of care processes or healthcare interactions per se (rather than the result of actions to alter risk factors) and medium to long-term outcomes in people with diabetes. Further work is still required to understand the nature of the association between receiving care process and mortality shown here. Even so, this work should be highly publishable and this work will soon be submitted for peer review.

Chapter 7: Variation in the risk of mortality in Type 1 and Type 2 diabetes by age at diagnosis: An analysis of the National Diabetes Audit in England

Introduction

Historically, Type 2 diabetes was considered a disease of middle to later life. Changes in lifestyle, particularly rises in obesity and physical inactivity, towards the end of the twentieth and at the beginning of the twenty-first century combined with an understanding that early diagnosis and management of Type 2 diabetes can improve long term outcomes means that an increasing number of people are being diagnosed with the disease in early adulthood.

A number of studies have found evidence of an additional risk of dying in people with Type 2 diabetes diagnosed in early adulthood compared to those diagnosed later in life [120–122]. Other studies have suggested that diagnosis of Type 2 diabetes in early adulthood has a similar association with mortality as Type 1 diabetes. However, relatively small cohort sizes and the inclusion of people diagnosed with diabetes prior to the big changes in management of Type 2 diabetes that followed the publication of trials in the late 1990s and early 2000s, specifically the impact of lower HbA1c and cardiovascular risk factor management (blood pressure and cholesterol) in reducing complications and mortality.

This analysis aims to assess if there are diagnostic age related differences in mortality risk between Type 1 and Type 2 diabetes in a large, representative and more contemporary 'real world' cohort.

Methods

The National Diabetes Audit combines data on people with diagnosed diabetes from primary and secondary care services. This provides a database of patient characteristics (type of diabetes, age, sex, ethnic group, social deprivation, smoking status). For these people the National Diabetes Audit collates once each year the latest valid recorded measurement of HbA1c, blood pressure, total cholesterol, body mass index and eGFR in the 15 month period running from January to March the following year. Using NHS numbers and year of birth people with Type 1 and Type 2 diabetes aged 20 years or older and recorded in the NDA as receiving care from an English NHS care provider after 1st January 2008 were matched to Office for National Statistics death registrations up to 31st December 2015. The earliest valid records of HbA1c, blood pressure,

cholesterol, body mass index and eGFR were identified to give an indication of cardiovascular risk as close as possible to diagnosis.

Statistical analyses

Cox regression models were created to compare survival between people diagnosed at similar ages with Type 1 diabetes and Type 2 diabetes. These models were adjusted for age, sex, smoking status, social deprivation, ethnic group, duration of diabetes, HbA1c, total cholesterol, diastolic and systolic blood pressure, body mass index and estimated glomerular filtration rate (eGFR).

Sensitivity analyses

The type of diabetes was identified using the latest recorded type of diabetes from healthcare records. In order to assess the impact of any potential misclassification of diabetes type in clinical records sensitivity analyses were carried out. Firstly, all individuals with a diagnosis of Type 1 diabetes where the first recorded body mass index was 30 kg/m^2 or greater were excluded from analysis. Secondly, all patients with a diagnosis of Type 2 diabetes and a first recorded body mass index of less than 25 kg/m2 were removed from the dataset. Thirdly, any person excluded from analysis in the two previous sensitivity analyses were simultaneously removed from calculations.

Results

The analysis included 44,334 people with Type 1 diabetes and 1,754,180 people with Type 2 diabetes. Of those with Type 1 diabetes 25,252 (57.0%) were diagnosed between the ages of 20 and 39 years whilst 124,548 (7.1%) of people with Type 2 diabetes were diagnosed in the same age range. The average follow up time for those with Type 1 diabetes was 5.8 years and 5.6 years for those with Type 2 diabetes. There were 3178 and 239,649 deaths among those with Type 1 and Type 2 diabetes respectively. Of these 559 were amongst those diagnosed with Type 1 diabetes between 20 and 39 years old and 1836 in people diagnosed with Type 2 diabetes in the same age group.

Amongst those diagnosed aged between 20 and 39 years old those with Type 2 diabetes had a higher body mass index, were less likely to be from White ethnic groups, and more likely to live in socially deprived neighbourhoods. Those diagnosed with Type 1 diabetes were more likely to be current smokers and had a higher first recorded HbA1c after diagnosis. As the age of diagnosis increases the difference in risk factors between those with Type 1 and Type 2 diabetes diminishes (see **Table 7.1**).

Table 7.1: Characteristics and risk factors by age of diagnosis and type of diabetes

	Age at diagnosis															
	Type 1 diabetes								Type 2 diabetes							
	20-39 years		40-49 years		50-59 years		60+ years		20-39 years		40-49 years		50-59 years		60+ years	
	n	%	n	%	n	%	n	%	N	%	n	%	n	%	n	%
Total	25,252		8,324		5,204		5,554		124,548		272,224		419,859		937,549	
Male	16,051	63.6%	5,437	65.3%	2,868	55.1%	2,772	49.9%	70,121	56.3%	166,128	61.0%	249,279	59.4%	487,545	52.0%
Age at start of follow up																
Mean	30.7		45.8		55.8		70.8		35.4		46.5		56.2		72.1	
Ethnic group																
White	18,251	72.3%	5,863	70.4%	3,642	70.0%	3,806	68.5%	60,543	48.6%	154,726	56.8%	268,468	63.9%	659,922	70.4%
Mixed	446	1.8%	109	1.3%	51	1.0%	38	0.7%	2,441	2.0%	4,119	1.5%	4,177	1.0%	5,347	0.6%
South Asian	1,209	4.8%	291	3.5%	223	4.3%	217	3.9%	27,586	22.1%	38,074	14.0%	40,740	9.7%	39,923	4.3%
Black	1,204	4.8%	451	5.4%	215	4.1%	170	3.1%	9,968	8.0%	19,392	7.1%	18,377	4.4%	25,969	2.8%
Other	1,038	4.1%	275	3.3%	185	3.6%	160	2.9%	10,180	8.2%	17,192	6.3%	19,899	4.7%	26,466	2.8%
Missing	3,104	12.3%	1,335	16.0%	888	17.1%	1,163	20.9%	13,830	11.1%	38,721	14.2%	68,198	16.2%	179,922	19.2%
IMD																
Most deprived	6,730	26.7%	1,967	23.6%	1,128	21.7%	1,074	19.3%	46,721	37.5%	85,754	31.5%	108,334	25.8%	188,934	20.2%
2nd most deprived	5,870	23.2%	1,765	21.2%	1,056	20.3%	1,086	19.6%	31,227	25.1%	64,415	23.7%	92,106	21.9%	189,626	20.2%
3rd most deprived	4,861	19.2%	1,656	19.9%	1,060	20.4%	1,198	21.6%	20,845	16.7%	49,240	18.1%	81,669	19.5%	197,441	21.1%
2nd least deprived	4,113	16.3%	1,507	18.1%	985	18.9%	1,129	20.3%	14,436	11.6%	39,352	14.5%	73,099	17.4%	191,634	20.4%
Least deprived	3,653	14.5%	1,422	17.1%	968	18.6%	1,060	19.1%	11,221	9.0%	33,313	12.2%	64,394	15.3%	169,179	18.0%
Missing	25	0.1%	7	0.1%	7	0.1%	7	0.1%	98	0.1%	150	0.1%	257	0.1%	735	0.1%
Body mass index at start																
<18.5	742	2.9%	157	1.9%	87	1.7%	101	1.8%	418	0.3%	571	0.2%	920	0.2%	6,480	0.7%
18.5-24.9	10,176	40.3%	2,584	31.0%	1,443	27.7%	1,354	24.4%	11,753	9.4%	19,768	7.3%	31,605	7.5%	128,228	13.7%
25-29.9	8,031	31.8%	2,897	34.8%	1,709	32.8%	1,808	32.6%	30,102	24.2%	68,444	25.1%	118,484	28.2%	335,008	35.7%
30-34.9	3,191	12.6%	1,479	17.8%	1,029	19.8%	1,211	21.8%	31,057	24.9%	78,087	28.7%	130,650	31.1%	266,171	28.4%
35-39.9	1,130	4.5%	584	7.0%	443	8.5%	453	8.2%	22,742	18.3%	52,565	19.3%	75,242	17.9%	113,064	12.1%
40+	660	2.6%	336	4.0%	253	4.9%	210	3.8%	24,471	19.6%	46,839	17.2%	54,050	12.9%	53,834	5.7%
Missing	1,322	5.2%	287	3.4%	240	4.6%	417	7.5%	4,005	3.2%	5,950	2.2%	8,908	2.1%	34,764	3.7%
Mean	26.0		27.5		28.1		28.2		33.5		33.3		32.4		30.0	

Smoking status at start																
Current smoker	8,550	33.9%	2,636	31.7%	1,228	23.6%	758	13.6%	31,607	25.4%	63,722	23.4%	84,379	20.1%	107,723	11.5%
Ex-smoker	3,624	14.4%	1,612	19.4%	1,237	23.8%	1,639	29.5%	19,775	15.9%	57,182	21.0%	117,827	28.1%	337,839	36.0%
Non-smoker	1,291	5.1%	495	5.9%	366	7.0%	492	8.9%	4,818	3.9%	12,058	4.4%	23,330	5.6%	65,476	7.0%
Never smoked	10,958	43.4%	3,351	40.3%	2,207	42.4%	2,419	43.6%	65,531	52.6%	134,687	49.5%	187,495	44.7%	403,460	43.0%
Missing	829	3.3%	230	2.8%	166	3.2%	246	4.4%	2,817	2.3%	4,575	1.7%	6,828	1.6%	23,051	2.5%
HbA1c, mmol/mol																
First recorded (mean)	70.2		67.8		65.5		59.6		61.8		59.1		55.8		51.8	
Blood pressure																
First recorded systolic (mean)	123.1		127.4		130.9		134.6		127.4		130.8		133.3		135.1	
First recorded diastolic (mean)	75.1		77.8		77.5		75.0		79.9		80.6		79.4		75.3	
Cholesterol (mol/l)																
First recorded (mean)	4.7		4.8		4.6		4.4		4.8		4.7		4.6		4.4	
eGFR																
90+	14,774	58.5%	3,599	43.2%	1,605	30.8%	760	13.7%	76,887	61.7%	124,798	45.8%	133,190	31.7%	132,743	14.2%
60-89	5,598	22.2%	2,814	33.8%	2,112	40.6%	2,159	38.9%	29,220	23.5%	98,422	36.2%	189,553	45.1%	416,767	44.5%
30-59	213	0.8%	218	2.6%	352	6.8%	1,098	19.8%	920	0.7%	5,535	2.0%	22,064	5.3%	183,936	19.6%
15-29	23	0.1%	14	0.2%	26	0.5%	95	1.7%	89	0.1%	298	0.1%	774	0.2%	8,065	0.9%
<15	9	0.0%	15	0.2%	14	0.3%	29	0.5%	61	0.0%	151	0.1%	303	0.1%	1,084	0.1%
Missing	4,635	18.4%	1,664	20.0%	1,095	21.0%	1,413	25.4%	17,371	13.9%	43,020	15.8%	73,975	17.6%	194,954	20.8%
Deaths	559	2.2%	513	6.2%	508	9.8%	1,598	28.8%	1,836	1.5%	7,200	2.6%	22,315	5.3%	208,298	22.2%

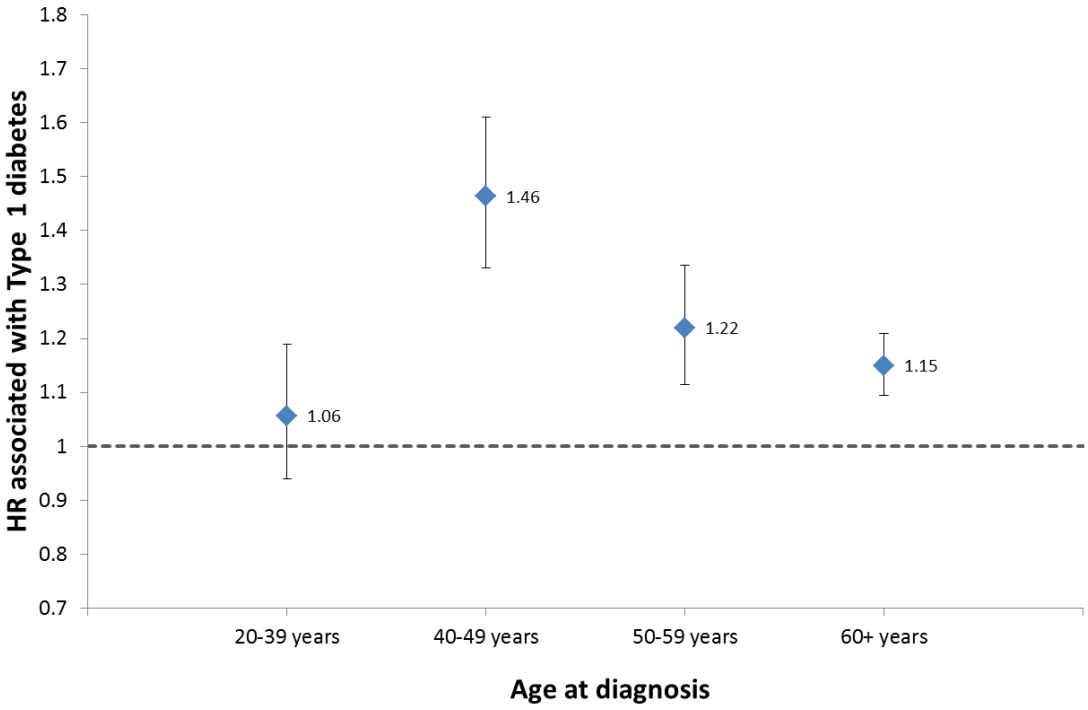
Across the whole cohort having a diagnosis of Type 1 diabetes compared to Type 2 diabetes was associated with a higher risk of mortality (HR 1.17, 95% CI 1.09-1.26). However, this association varied by age of diagnosis. Amongst those diagnosed aged between 20 and 39 years old, having Type 1 diabetes rather than Type 2 diabetes is not associated with an additional risk of dying after adjusting for demographic characteristics and cardiovascular risk factors (HR 1.06, 95% CI 0.94-1.19). Type 1 diabetes rather than Type 2 diabetes is associated with higher mortality in those diagnosed aged 40 to 49 years old (HR 1.46, 95% CI 1.33-1.61) and aged 50 to 59 years old (HR 1.22 95% CI 1.12-1.34). The additional risk of dying associated with a diagnosis of Type 1 diabetes (compared to Type 2 diabetes) among people diagnosed aged 60 years and older is lower but still statistically significant (HR1.15 95% CI 1.09-1.21).

If people with a diagnosis of Type 1 diabetes and a first recorded body mass index of 30kg/m2 or greater were excluded from the analysis the hazard ratio associated with a diagnosis of Type 1 diabetes changed to 0.91 remained not statistically significant (95% CI 0.78-1.05) in the 20-39 years age group. All other results of the sensitivity analysis remained similar to the original model (see **Table 7.2**).

Table 7.2: Sensitivity analysis – hazard ratios associated with Type 1 diabetes relative to those with Type 2 diabetes

	20-39 years	40-49 years	50-59 years	60+ years
Base analysis	1.06 (0.94-1.19)	1.46 (1.33-1.61)	1.22 (1.12-1.34)	1.15 (1.09-1.21)
T1 sensitivity	0.91 (0.78-1.05)	1.35 (1.20-1.52)	1.17 (1.04-1.31)	1.13 (1.06-1.21)
T2 sensitivity	1.09 (0.95-1.25)	1.61 (1.45-1.78)	1.27 (1.15-1.40)	1.20 (1.13-1.26)
T1 and T2 sensitivity	1.04 (0.83-1.22)	1.57 (1.39-1.78)	1.23 (1.09-1.39)	1.14 (1.06-1.22)

Figure 7.1: Hazard ratios associated with Type 1 diabetes by age of diagnosis relative to those with Type 2 diabetes



Discussion

This analysis has considered how the risk of medium term mortality compares between people with Type 1 and Type 2 diabetes. Type 1 diabetes has traditionally been seen to have a larger detrimental impact on morbidity and mortality than Type 2 diabetes. However, the results presented above show that when Type 2 diabetes is diagnosed between the ages of 20 and 39 years there is no significant difference after adjustment for demographic characteristics and cardiovascular risk factors. This analysis suggests that diagnosis of Type 2 diabetes in early adulthood is equivalent to diagnosis of T1 diabetes in terms of medium mortality risk. An Australian study if 824 people diagnosed with diabetes between the ages of 15 and 30 years old found that those with Type 2 diabetes had a greater absolute and risk factor adjusted mortality rate than those diagnosed with Type 1 diabetes over a follow up period of over 20 years [120]. However this recruitment to this cohort dates back to 1986 and there have been considerable shifts in the approach to managing diabetes, in particular Type 2 diabetes, over the follow up period which may explain the different findings to this analysis. Another study in India reported

outcomes of 108 people with Type 1 diabetes and 90 with Type 2 diabetes diagnosed between the ages of 10 and 25 years after five years follow up. After age, HbA1c, blood pressure and cholesterol those with Type 2 diabetes were approximately twice as likely to develop a diabetes related complication. The small cohort size and very different patient characteristics and healthcare systems in England and India make it difficult to unpick the reasons for the potentially different outcomes in these studies.

One of the strengths of this work is the large cohort size which reflects real world clinical practice and outcomes. Everyone included in the analysis has been diagnosed with diabetes since 2008. This means that they have been treated in the current paradigm of diabetes management for the duration of their condition. The mean follow up period for this analysis was 5.8 years for those with Type 1 diabetes and 5.6 years for those with Type 2 diabetes. A longer follow up period would provide further insight into the lifetime risks associated with a diagnosis of diabetes at various ages. In particular, as those diagnosed in early adulthood move towards middle and later life their absolute risk of cardiovascular events and death will increase and the full impact of the potential association between age of diagnosis and outcomes will be clearer.

The National Diabetes Audit is reliant on data recorded in clinical systems. This includes the type of diabetes but this classification is dependent on accurate identification and recording. Type of diabetes is usually verified by cross-referencing with drug prescription data. As the National Diabetes Audit does not currently collect this information, a sensitivity analysis based on the first body mass index measurement recorded after diagnosis was undertaken. The fact this analysis did not substantially alter the study findings strengthens their validity.

Is early diagnosis of Type 2 diabetes equivalent to diagnosis of Type 1 in terms of risk of dying? This study appears to suggest that this is the case but further analysis over a longer time and considering a range of diabetes related outcomes is required to provide a more definitive answer. Emerging evidence from Sweden suggests that those who develop Type 2 diabetes in adolescents lose well over a decade of life expectancy [123], which is on a par with Type 1 development at the same age [124] using from data from same country. These findings in NDA suggest that whilst excess risk declines with age of diagnosis in

Type 2 once people reach their 40s and older, it may be that such risks do not decline as much in people who develop Type 1 diabetes in their 40s and onwards, so explaining their higher risks in this age group. Repeating these analyses once we have data for drugs prescribed as it may be that people diagnosed with Type 1 diabetes in middle age are not treated as aggressively as those developing Type 2 diabetes. Certainly, some guidelines are less aggressive in their recommendations for preventative therapies [125] for this group than in those with Type 2 diabetes.

Update

A literature review conducted after the production of this chapter did not identify any further population based analyses comparing medium to long term outcomes among people with Type 1 and Type 2 diabetes. As from 2017/18 onwards the NDA includes data on prescriptions for glucose lowering drugs, anti-hypertensive medications and statins there would be scope for future analyses to validate the classification of types of diabetes and consider how the management of cardiovascular risk factors mediates the additional risk of death experienced by those diagnosed with diabetes in early adulthood. This would strengthen the methodology and potentially add to the understanding of mortality risk for those who live, or are likely to live, with diabetes for many decades. In the meantime, it is clear that other national cohorts need to replicate our novel findings. This work will be submitted for peer review in the near future.

Chapter 8: Age at diagnosis, ethnic group and mortality in people with Type 2 diabetes: Analysis of the National Diabetes Audit in England

Introduction

Historically, Type 2 diabetes was considered a disease of middle to later life. Changes in lifestyle, particularly rises in obesity and physical inactivity, towards the end of the twentieth and at the beginning of the twenty-first century combined with an understanding that early diagnosis and management of Type 2 diabetes can improve long term outcomes means that an increasing number of people are being diagnosed with the disease in early adulthood.

A number of studies have found evidence of an additional risk of cardiovascular events or dying in people with Type 2 diabetes diagnosed in early adulthood compared to those diagnosed later in life [121,126,127]. However, relatively small cohort sizes and the inclusion of people diagnosed with diabetes prior to the big changes in management of Type 2 diabetes that followed the publication of trials in the late 1990s and early 2000s, specifically the impact of lower HbA1c and cardiovascular risk factor management (blood pressure and statins) in reducing complications and mortality.

This analysis is able to assess whether there are associations between age at diagnosis of Type 2 diabetes and mortality in a large, representative and more contemporary 'real world' cohort. It looks at whether there are diagnostic age related differences in additional mortality and between ethnic groups In England.

Methods

The National Diabetes Audit combines data on people with diagnosed diabetes from primary and secondary care services. This provides a database of patient characteristics (age, sex, ethnic group, social deprivation, smoking status). For these people the National Diabetes Audit collates once each year the latest valid recorded measurement of HbA1c, blood pressure, total cholesterol, body mass index and eGFR in the 15 month period running from January to March the following year. Using NHS numbers and year of birth people with Type 1 and Type 2 diabetes aged 20 years or older and recorded in the NDA as receiving care from an English NHS care provider after 1st January 2008 were matched to Office

for National Statistics death registrations up to 31st December 2015. The earliest valid records of HbA1c, blood pressure, cholesterol, body mass index and eGFR were identified to give an indication of cardiovascular risk as close as possible to diagnosis.

Statistical analyses

The statistical significance of differences in the characteristics of people diagnosed with Type 1 and Type 2 diabetes by age of diagnosis was identified using chi-square tests for categorical variables.

Cox regression models were created to explore the association between age at diagnosis and mortality after adjusting for

- Age and sex
- Age, sex and smoking status
- Age, sex, smoking status, social deprivation as measured by the Indices of multiple Deprivation (IMD) and ethnic group
- Age, sex, smoking status, social deprivation, ethnic group, duration of diabetes and HbA1c
- Age, sex, smoking status, social deprivation, ethnic group, duration of diabetes and HbA1c, total cholesterol, diastolic and systolic blood pressure
- Age, sex, smoking status, social deprivation, ethnic group, duration of diabetes and HbA1c, total cholesterol, diastolic and systolic blood pressure, body mass index and estimated glomerular filtration rate (eGFR)

Diagnosis over the age of 60 years was used as a reference category.

To assess whether the relationship between age of diagnosis and mortality risk varied by ethnic group separate models were created for people from white ethnic groups (White British, White Irish and White 'other' groups), from south Asian ethnic groups (Indian, Pakistani and Bangladeshi) and from Black ethnic groups (Black African and Black Caribbean).

Models were created to compare survival between people diagnosed at similar ages with Type 1 diabetes and Type 2 diabetes. These models adjusted for age, sex, smoking status, social deprivation, ethnic group, duration of diabetes, HbA1c, total cholesterol, diastolic and systolic blood pressure, body mass index and estimated glomerular filtration rate (eGFR).

Results

The analysis included 1,754,180 people with Type 2 diabetes, of which 124,548 (7.1%) were diagnosed between the ages of 20 and 39 years old. The average follow up time was 5.6 years and there were 239,649 deaths.

When compared with people diagnosed with Type 2 diabetes aged 60 years and older those diagnosed between the ages of 20 and 39 years old were less likely to be from White ethnic groups (48.6% vs 72.3%, $p<0.005$), more likely to live in the most deprived fifth of neighbourhoods (37.5% vs 26.7%, $p<0.005$), more likely to have a higher body mass index (mean 33.5 vs 26.0) and less likely to be a current smoker (25.4% vs 33.9%, $p<0.005$) (see **Table 8.1**).

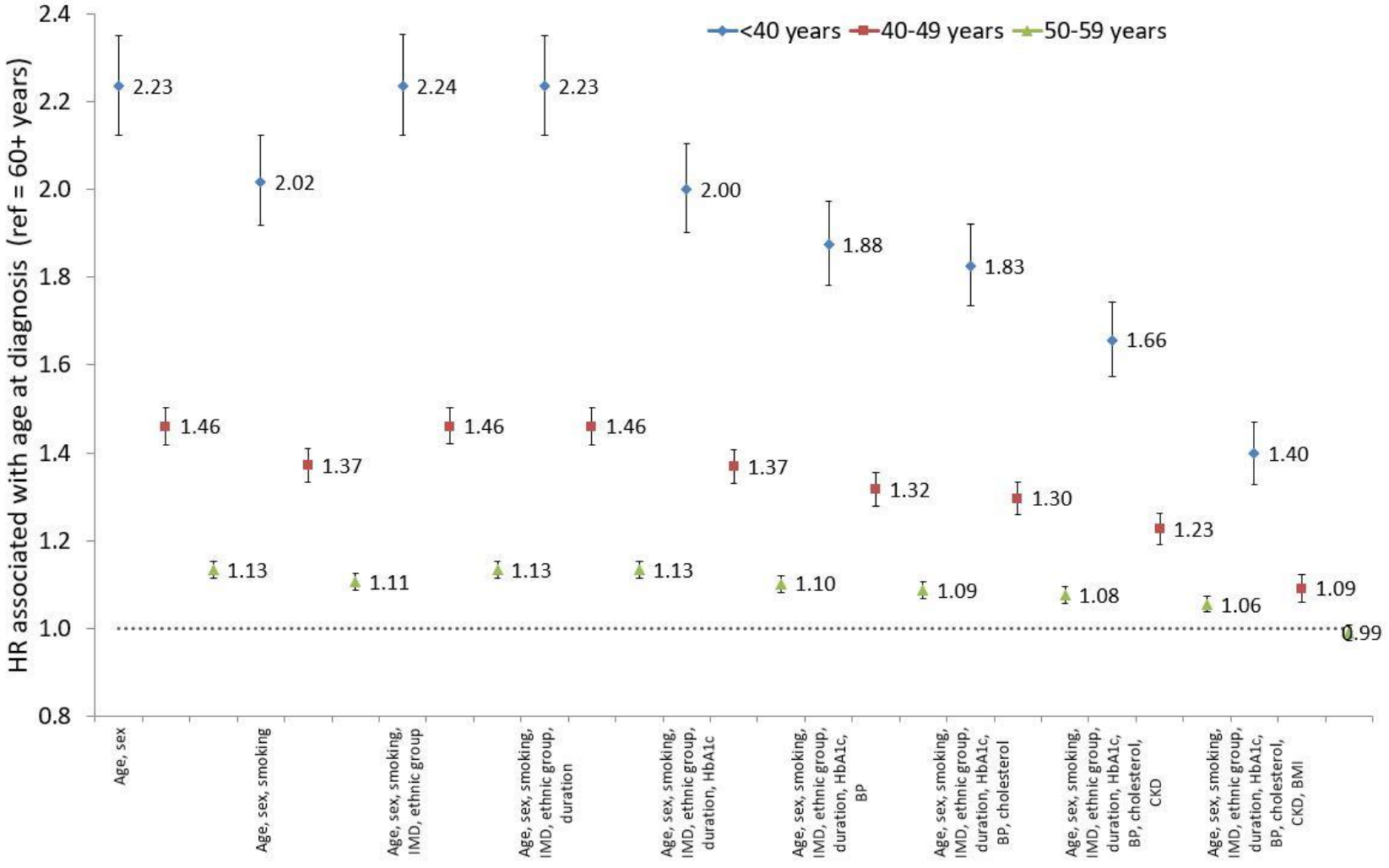
Table 8.1: Characteristics by age of diagnosis of Type 2 diabetes

	20-39 years		40-49 years		50-59 years		60+ years	
	n	%	n	%	n	%	n	%
Total	124,548		272,224		419,859		937,549	
Male	70,121	56.3%	166,128	61.0%	249,279	59.4%	487,545	52.0%
Age at start of follow up								
Mean(years)	35.4		46.5		56.2		72.1	
Ethnic group								
White	60.543	48.6%	154.726	56.8%	268.468	63.9%	659.922	70.4%
South Asian	2.441	2.0%	4.119	1.5%	4.177	1.0%	5.347	0.6%
Black	27.586	22.1%	38.074	14.0%	40.740	9.7%	39.923	4.3%
Mixed	9.968	8.0%	19.392	7.1%	18.377	4.4%	25.969	2.8%
Other	10.180	8.2%	17.192	6.3%	19.899	4.7%	26.466	2.8%
Missing	13.830	11.1%	38.721	14.2%	68.198	16.2%	179.922	19.2%
IMD								
Most deprived	46,721	37.5%	85,754	31.5%	108,334	25.8%	188,934	20.2%
2nd most deprived	31,227	25.1%	64,415	23.7%	92,106	21.9%	189,626	20.2%
3rd most deprived	20,845	16.7%	49,240	18.1%	81,669	19.5%	197,441	21.1%
2nd least deprived	14,436	11.6%	39,352	14.5%	73,099	17.4%	191,634	20.4%
Least deprived	11,221	9.0%	33,313	12.2%	64,394	15.3%	169,179	18.0%
Missing	98	0.1%	150	0.1%	257	0.1%	735	0.1%
Body mass index (kg/m^2)								
<18.5	418	0.3%	571	0.2%	920	0.2%	6,480	0.7%
18.5-24.9	11,753	9.4%	9,768	7.3%	31,605	7.5%	128,228	13.7%
25-29.9	30,102	24.2%	68,444	25.1%	118,484	28.2%	335,008	35.7%
30-34.9	31,057	24.9%	78,087	28.7%	130,650	31.1%	266,171	28.4%
35-39.9	22,742	18.3%	52,565	19.3%	75,242	17.9%	113,064	12.1%
40+	24,471	19.6%	46,839	17.2%	54,050	12.9%	53,834	5.7%
Missing	4,005	3.2%	5,950	2.2%	8,908	2.1%	34,764	3.7%
Mean	33.5		33.3		32.4		30.0	
Smoking status at start								
Current smoker	31,607	25.4%	63,722	23.4%	84,379	20.1%	107,723	11.5%
Ex-smoker	19,775	15.9%	57,182	21.0%	117,827	28.1%	337,839	36.0%
Non-smoker	4,818	3.9%	12,058	4.4%	23,330	5.6%	65,476	7.0%
Never smoked	65.531	52.6%	134.687	49.5%	187.495	44.7%	403.460	43.0%
Missing	2.817	2.3%	4.575	1.7%	6.828	1.6%	23.051	2.5%
HbA1c, mmol/mol								
First recorded (mean)	61.8		59.1		55.8		51.8	
Blood pressure (mmHg)								
First recorded systolic	127.4		130.8		133.3		135.1	
First recorded diastolic	79.9		80.6		79.4		75.3	
Cholesterol (mol/l)								
First recorded (mean)	4.8		4.7		4.6		4.4	
eGFR								

90+	76.887	61.7%	124.798	45.8%	133.190	31.7%	132.743	14.2%
60-89	29.220	23.5%	98.422	36.2%	189.553	45.1%	416.767	44.5%
30-59	920	0.7%	5.535	2.0%	22.064	5.3%	183.936	19.6%
15-29	89	0.1%	298	0.1%	774	0.2%	8.065	0.9%
<15	61	0.0%	151	0.1%	303	0.1%	1.084	0.1%
Missing	17,371	13.9%	43,020	15.8%	73,975	17.6%	194,954	20.8%
Deaths	1,836	1.5%	7,200	2.6%	22,315	5.3%	208,298	22.2%

Diagnosis of Type 2 diabetes between the ages of 20 and 39 years old compared to aged 60 years and over is associated with a hazard ratio of mortality of 2.23 (95% CI 2.12-2.35, adjusted for age and sex) **Figure 8.1**.

Figure 8.1: Hazard ratios for mortality associated with age of diagnosis of Type 2 diabetes



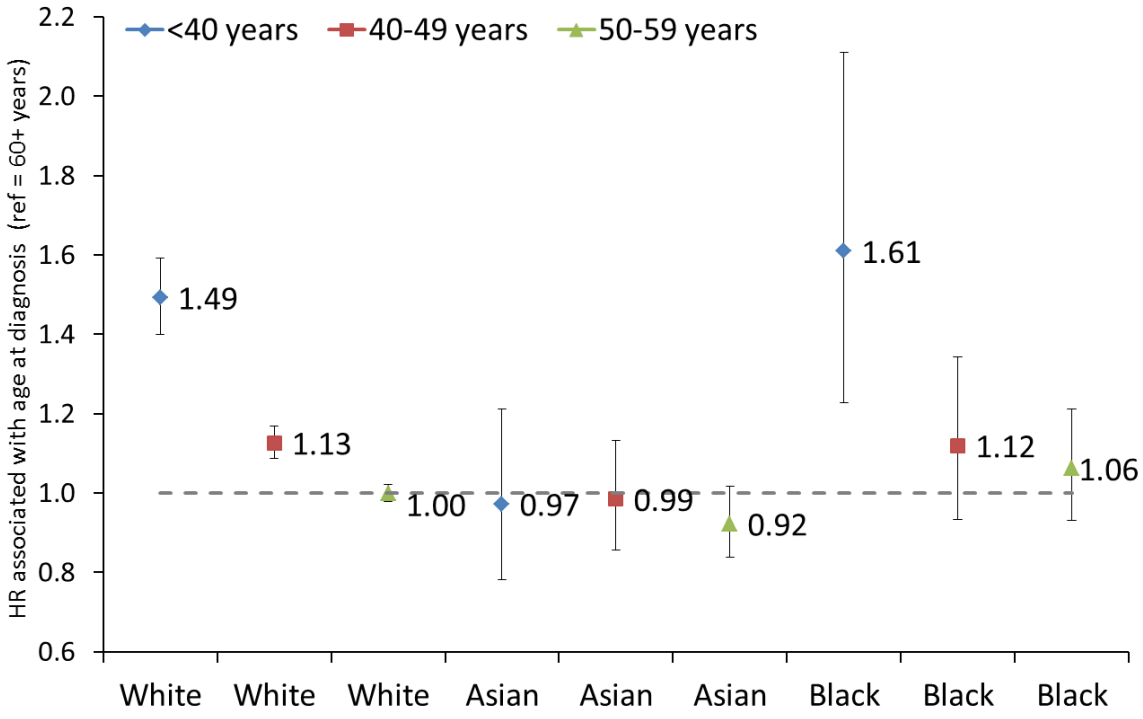
Adjustment for demographic characteristics (social deprivation, ethnic group) and smoking status does not alter this association (HR 2.24, 95% CI 2.12-2.35). Further adjustment for duration of diagnosed diabetes and first recorded HbA1c reduces the additional risk of death (HR 2.00, 95% CI 1.90-2.11). Extending the model to include all available risk factors (first recorded blood pressure, cholesterol, body mass index and eGFR) further attenuates the additional risk of dying associated with diagnosis in early adulthood (HR 1.40, 95% CI 1.33-1.47). A significant but lower additional risk of mortality is found when those diagnosed aged 40 to 49 years old are compared to those diagnosed over the age of 60 (HR 1.46, 95% CI 1.42-1.50 when adjusting for age and sex, HR 1.09, 95% CI 1.06-1.12 when adjusting for all available risk factors). When those diagnosed aged between 50 and 59 years old are compared to those diagnosed aged 60 and over there is an additional risk of dying after adjusting for age and sex(HR 1.13, 95% CI 1.11-1.15) but this is removed once adjustment includes cardiovascular risk factors (HR 0.99, 95% CI 0.97-1.01 when adjusting for all available risk factors). After adjustment for demographic characteristics (age, sex, social deprivation) and cardiovascular risk factors (smoking, duration of diabetes, HbA1c, blood pressure, cholesterol, body mass index and eGFR) younger age at diagnosis of Type 2 diabetes is associated with higher medium term mortality in those from White ethnic groups (see **Table 8.2** and **Figure 8.2**).

Table 8.2: Hazard ratios associated with age of diagnosis of Type 2 diabetes by ethnic group

		White	Asian	Black
		HR (95% CI)	HR (95% CI)	HR (95% CI)
Age at diagnosis	<40	1.49 (1.40-1.59)	0.93 (0.78-1.21)	1.61 (1.23-2.11)
	49-49	1.13 (1.09-1.17)	0.99 (0.86-1.13)	1.12 (0.93-1.34)
	50-59	1.00 (0.98-1.02)	0.92 (0.84-1.02)	1.06 (0.93-1.21)
	60+	Reference group	Reference group	Reference group

After adjustment for age, sex, smoking, social deprivation, ethnic group, duration, HbA1c, blood pressure, cholesterol, body mass index and eGFR

Figure 8.2: Hazard ratios associated with age of diagnosis of Type 2 diabetes by ethnic group



When compared to diagnosis aged 60 years and older being diagnosed with Type 2 diabetes between the aged of 20 and 39 years was associated with a higher risk of death after adjustment for demographic characteristics and cardiovascular risk factors (HR 1.61, 95% CI 1.23-2.11) in people from Black ethnic groups. The additional risks of death associated with diagnosis of Type 2 diabetes between the ages of 40 to 49 and 50 to 59 years old compared to aged 60 years and older in people from Black ethnic groups were not statistically significant (see **Table 8.2** and **Figure 8.2**). There was no statistically significant association between age of diagnosis of Type 2 diabetes and risk of mortality amongst those from South Asian ethnic groups (HR 0.97 for those diagnosed aged 20 to 39 years old compared to aged 60 years and older, 95% CI 0.78-1.12).

Discussion

The analysis of this large observational dataset has shown that diagnosis of Type 2 diabetes in early adulthood is associated with a higher risk of dying over the medium term compared to diagnosis in later life. Some of this additional risk of mortality is explained by the poorer cardiovascular risk profiles of people diagnosed at younger ages. However, even after adjustment for established risk

factors the additional risk of dying remains considerable (HR 1.40, 95% CI 1.33-1.47). This supports the suggestion that Type 2 diabetes that develops in early adulthood is a different and more deadly phenotype than occurs in people who are diagnosed in later life.

Some previous studies have provided tentative evidence of greater risks associated with Type 2 diabetes diagnosed in early adulthood. An Australian study of 354 people diagnosed with Type 2 diabetes between the ages of 15 and 29 years found they had mortality rates three times greater than the general population (SMR 3.4 95% CI 2.7-4.2). They reported that as the age of diagnosis increased the additional risk of mortality in those with type 2 diabetes compared to the general population declined [121]. However, this study did not adjust for cardiovascular risk profile and covers those diagnosed from 1986 onwards and therefore covers a long period of time during which the approach to managing Type 2 diabetes has changed significantly. This study showed that people diagnosed with Type 2 diabetes in early adulthood had a poorer cardiovascular risk profile than those diagnosed at older ages. A recent analysis of over 100,000 people with Type 2 diabetes in Sweden has also highlighted that those that were diagnosed at younger ages had a poorer cardiovascular risk profile (more frequently obese, more adverse lipid profile and a higher HbA1c). It also reports that those diagnosed at a young age (aged 18 to 44 years) experienced a faster deterioration in glycemic control than those who developed diabetes later in life [127].

This is perhaps the first study to consider how characteristics and outcomes in people with diabetes vary by age at diagnosis in different ethnic groups. The association between younger age at diagnosis of Type 2 diabetes and a greater mortality risk is statistically and clinically significant for people from White and Black ethnic groups but no such association was found amongst those from South Asian ethnic groups. This suggests that early diagnosis of Type 2 diabetes is not detrimental to mortality when compared to diagnosis in later life. Previous studies have shown that South Asian people with Type 2 diabetes and in the general population have a lower risk of dying than their peers from White ethnic groups [128]. Further analysis over a longer time period would be required to explore this finding further and elucidate potential explanations for the

seemingly different risk of dying among people with Type 2 diabetes from South Asian groups. In particular it would be useful to consider how trajectories of glycaemic control vary in different ethnic groups and potential interactions with other cardiovascular risk factors.

The strength of this work lies in the large cohort of people included in the analysis and the fact that it represents a 'real world' setting collating data from routine clinical practice. In particular, this has enabled the variation in risk by ethnic group to be considered. It is also important to note that everyone included in this analysis has been diagnosed over a relatively short period during the current paradigm of diabetes management with a particular emphasis on intensive cardiovascular risk management in order to reduce current and future cardiovascular risk.

This study is limited by the lack of data on prescribed medication. It is also limited by lack of data on people without diabetes, as others have recently published [123] and showed similar higher excess risks in those diagnosed with Type 2 at younger ages. It is possible that some of the additional risk of mortality shown in people who have been diagnosed with Type 2 diabetes in early adulthood can be explained by variation in the use of prescribed medication and the management of cardiovascular risk in this group. Variation in either prescribing or drug efficacy by ethnic group should also be considered. The National Diabetes Audit has recently started to collect data on prescribed drugs and associated items [129]. In time, this will provide a valuable data source to examine further the high mortality risk experienced by those who develop Type 2 diabetes at relatively young ages.

Whilst the follow up period for the cohort is reasonable, (mean 5.6 years), a longer follow up period would yield greater insight into difference in risk experienced depending on age at diagnosis. In particular, it would be interesting to follow those diagnosed at younger ages as they proceed through middle and later life and consider their cardiovascular risk trajectories and morbidity. As population and societal changes continue the increasing proportion of people with Type 2 diabetes who develop the disease in early adulthood is likely to increase, and clinicians are already starting to see more

and more people under 40 with newly diagnosed type 2 diabetes. If these people continue to experience additional risks this is likely to result in greater need for health and social care over the coming decades. Further research to understand these risks is crucial to inform potentially differing diabetes clinical management strategies and prioritisation of scare health care resources.

Update

Since the production of this chapter an analysis of the Australian National Diabetes Audit has reported that people with Type 2 diabetes under the age of 64 showed poorer patterns of self-care (physical activity, following dietary recommendations, medication adherence and monitoring blood glucose levels) than those aged 64 and older. Within this cohort those in the younger age group also showed poorer glycemic control with 76% having a HbA1c of more than 53mmol/mol compared to 68% in the older age group [130]. The role of individual self-care behaviors and the extent to which its full effect is captured by routinely monitored risk factors should be considered in explaining the higher medium term mortality amongst those diagnosed at younger ages noted in this chapter. Our work needs replication in other national cohorts as it adds more questions than answers. That there is no clear gradient of cardiovascular risk by age of Type 2 diagnosis in South Asians is intriguing but we acknowledge this finding needs replication as well as an investigation into potential mechanisms if the findings are indeed validated by others.

Chapter 9: Discussion

This thesis is a collation of studies assessing current patterns of processes of care and outcomes for people in England with diabetes that have used data routinely collated as part of clinical care. It provides a picture of the 'real world' outcomes for those with diabetes and highlights some of the methodological considerations when using data that has not been collected specifically for research purposes.

The use of routinely collated data for research purposes creates an efficient way to consider outcomes for large cohorts of people. It allows outcomes of 'real world' populations to be considered rather than the often highly selected cohorts included in specific research studies that tend to be younger, have fewer co-morbidities and potentially have a different approach to the management of their health to the complete group of people with diabetes. Bespoke data collection on the scale required to create the study populations used in the analyses presented in this thesis would be costly and impractical. There is also a value in considering the actual and perceived ownership of data in how the results of research are presented to and received by clinicians working in diabetes care. The presentation of the analysis of mortality among inpatients with diabetes (Chapter 3) to clinicians was initially met with criticisms of the dataset and methodology. However, further discussion led to reflection and an understanding of the need to engage with routine data collection to ensure it accurately reflects clinical practice and outcomes.

Despite the advantages, there are also drawbacks to the use of these type of data. The accuracy and completeness of the data can be variable over time and place. It can be subject to changes in definition or interpretation and may also be subject to organisational and financial incentives. One of the challenges of using data originally collected for administrative purposes is not being able to define the data variables. In Chapter 5 data on people presenting with diabetic foot ulcers in Salford are analysed. This included data on four of the six dimensions of the externally validated and widely used SINBAD score. As a result, the analysis used a measure of ulcer severity that was as close an approximation as possible. Whilst this provides a useful measure of foot ulcer severity being able to use a validated tool and make more direct comparisons with other studies would have improved the interpretation of the results and allowed more meaningful discussion. Similarly, the National Diabetes Audit

collates the latest valid result from clinical care processes in a 15-month audit period. Chapters 7 and 8 consider a cohort of people with newly diagnosed diabetes and aimed to adjust for established cardiovascular risk factors. An ideal analysis would assess and adjust for risk factors at the time of diagnosis but the nature of the data collection means that the earliest available measurements may be up to 15 months after this point. Similarly validation of the type of diabetes recorded in the National Diabetes Audit was limited to cross referencing with body mass index measurements when linking to drug prescription data would have provided a more robust approach. Despite the restrictions of data defined and collected for other purposes analysis can be useful in generating hypotheses although a pragmatic approach is often needed.

This work has aimed to consider contemporary outcomes for people with diabetes. Sometimes it is easiest to measure the process of healthcare (eg the number of procedures undertaken) rather than actual outcomes, in particular those that are most meaningful to patients. This can be particularly true when using datasets whose primary purpose is administrative and financial. Chapter 5 reports the pilot work to develop a national data collection process and analysis plan for people with diabetic foot disease. Much of the previous study in this area had used lower limb amputations as an outcome measure. However, this a measure of treatment process and does not accurately capture the outcome of an episode of ill health from the perspective of the patient. It was therefore a very deliberate decision to include a measure of quality of life in the data collection and this provided useful additional information on outcomes.

Previous analysis of the National Diabetes Audit shows how current cardiovascular risk factors compare to those reported in the landmark studies undertaken at the end of the 20th century that shape the current approach to diabetes management [47]. The fact that the current population wide outcomes for people recently diagnosed with Type 2 diabetes are similar to those achieved amongst a highly selected group receiving intensive care as part of a research study is a considerable achievement. The publication of the UKPDS study coincided with the first change in the national governing party in a generation. This lead to a paradigm shift in healthcare with a greater emphasis on preventative medicine and the proactive management of long-term conditions. However, over the next couple of decades the nature of diabetes care is likely to

change. Current lifestyle trends towards inactivity and obesity in conjunction with demographic changes and improvements in mortality are leading to higher prevalence of Type 2 diabetes, in particular amongst younger adults. Chapters 7 and 8 explored the variation in mortality by age of diagnosis and supported previous studies that have highlighted the poor outcomes associated with the diagnosis of Type 2 diabetes in early adulthood. However, the suggestion that there are significant differences in this association between ethnic groups requires further investigation. Even so, the rising number of diabetes patients at both ends of the age scale, and particularly those who are younger and more obese, poses great challenges over the next few decades in the UK. This means that primary and secondary prevention will increasingly be the way to improve outcomes and minimise the societal and financial costs of diabetes. Furthermore, rising prevalence of diabetes and its complications in low and middle-income countries due to changes in lifestyle will lead to major human and financial challenges for societies throughout the world.

Going forwards

Given my knowledge of the epidemiology of diabetes and experience in analysing the NDA, I have been fortunate to win further funding from Diabetes UK to run additional analyses on this cohort. This will include working in conjunction with an advisory group of clinicians with relevant clinical and epidemiological expertise, including some of my supervisors for my thesis. Whilst not a comprehensive list, some of the further analyses I will purse include the following:

1. I have begun to look at number of people who may have undergone remission of Type 2 diabetes. This is a complex analysis which makes use of the newly collated drugs data. It is of great importance given the recent results of the DIRECT trial [131] as well as an increasing focus on lifestyle changes that are taking place in the National Diabetes Prevention Programme.

2. There is increasing interest in heart failure and to this end, we have a potential to look at how common heart failure is, trends in incidence and

potential changes in the association between risk factors over time in people with diabetes. We will also look at the commonest first vascular presentation in diabetes patients without prior cardiovascular disease to see if we can verify that heart failure and peripheral vascular disease are becoming more common first presentations, as suggested by a recent seminal report based on two million patients [132].

3. As data on prescriptions for glucose lowering, anti-hypertensive and statin drugs are becoming available through the NDA the scope of analysis will expand. There will be potential to undertake pharmacoepidemiological analyses which will have great statistical power given the large size of the NDA which is substantially bigger than Scottish, Swedish or indeed many other datasets with similar level of linkage. Of course, longer follow-up will be needed to enable sufficient follow up to look at outcomes as these numbers increase over time from the point when drug data became available and the impact of exposure over time becomes identifiable. In the meantime, we can have the ability to examine patterns of drug prescription, which has assumed greater importance given the rise in the use of newer diabetes drugs in the SGLT2i and GLP-1RA classes.

4. There will be multiple other ideas to pursue and there is also the potential to collaborate with other national datasets in analyses that are mutually beneficial. For example, my supervisors have links to Swedish, Danish and Scottish Registries and in some cases, there is a need to replicate findings in other countries to confirm patterns.

Overall, I am confident that with the knowledge I have accumulated working on this thesis, including all the obstacles we had to overcome, as well as all the links I have made, I am ideally placed to make a meaningful contribution to future diabetes care epidemiology.

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