A study of the descriptive epidemiology and clinical effectiveness of treatment for type 2 diabetes using routine general practice data

A thesis submitted for the degree of

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by

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Summary

The prevalence of type 2 diabetes is increasing in the UK. Many people with type 2 diabetes require glucose-lowering therapy including insulin when lifestyle interventions fail to provide adequate glucose control. Some epidemiological studies report an association between insulin use in type 2 diabetes and an increased risk of serious adverse events when compared with other glucose-lowering therapies. However, these findings should be interpreted with caution due to the risk of confounding by indication. The aim of this thesis was to characterise the epidemiology of type 2 diabetes and to investigate the risk of serious adverse events associated with increasing insulin dose in people with type 2 diabetes prescribed insulin therapy.

A series of retrospective, observational studies were conducted using data from the Clinical Practice Research Datalink. People with type 2 diabetes were identified and prevalence and incidence rates calculated. The risk of all-cause mortality, major cardiovascular events and cancer in people with type 2 diabetes who progressed to insulin with or without metformin were evaluated using multivariate models.

Between 1991 and 2010, the estimated incidence and prevalence of clinically diagnosed and recorded type 2 diabetes increased three-fold. During the same period, the estimated number of people with diagnosed and recorded type 2 diabetes treated with insulin increased seven-fold.

Estimated insulin dose was associated with an increased risk of all-cause mortality in people with type 2 diabetes receiving insulin monotherapy (aHR 1.54, 95% CI 1.32–1.78, for 1 unit/kg/day increase in insulin dose) and in those treated with insulin with or without metformin (1.48, 1.31–1.70). However, the use of metformin in

combination with insulin was associated with a reduction in risk compared with insulin alone (0.60, 0.52–0.68).

Due to the limitations associated with observational studies, further research is required in order to improve our understanding of the risks and benefits of exogenous insulin in type 2 diabetes.

Publications and presentations arising from this thesis

Publications

1. Holden SE, Jenkins-Jones S, Morgan CL, Schernthaner G, Currie CJ. Glucose-lowering with exogenous insulin monotherapy in type 2 diabetes: dose association with all-cause mortality, cardiovascular events, and incident cancer. Diabetes Obes Metab 2015 17:350-62.
2. Currie CJ, Holden SE. Optimising clinical outcomes resulting from glucose lowering therapies in type 2 diabetes: increased confidence about the DPP-4 inhibitors and continued concerns regarding sulfonylureas and exogenous insulin. Diabetes Obes Metab 2014;16:881-4.
3. Holden S, Currie C. Insulin therapy in people with type 2 diabetes: is it safe in terms of the risk of cardiovascular disease, cancer and all-cause mortality? *Diabetes Voice* 2014;59:40–41.
4. Holden SE, Currie CJ. Mortality risk with sulfonylureas compared to metformin. *Diabetes Obes Metab* 2014;16:885-90.
5. Holden SE, Gale EA, Jenkins-Jones S, Currie CJ. How many people inject insulin? UK estimates from 1991 to 2010. *Diabetes Obes Metab* 2014;16:553-9.
6. Holden SE, Barnett AH, Peters JR, Jenkins-Jones S, Poole CD, Morgan CL, Currie CJ. The incidence of type 2 diabetes in the United Kingdom from 1991 to 2010. *Diabetes Obes Metab* 2013;15:844-852.
7. Holden SE, Currie CJ. Endogenous hyperinsulinaemia and exogenous insulin: a common theme between atherosclerosis, increased cancer risk and other morbidities. *Atherosclerosis* 2012;222:26-28.

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9. Holden SE, Poole CD, Morgan CL, Currie CJ. Evaluation of the incremental cost to the National Health Service of prescribing analogue insulin. *BMJ Open* 2011;1: e000258.

Conference proceedings

1. Holden SE, Jenkins-Jones S, Morgan CL, Schernthaner G, Currie CJ. Glucose-lowering with exogenous insulin monotherapy in type 2 diabetes: dose-response association with all-cause mortality, cardiovascular events, and incident cancer. Value In Health 2014;17:A240-A240.
2. Holden SE, Currie CJ. The impact of concomitant metformin on mortality and other serious outcomes in people with type 2 diabetes treated with insulin. Value In Health 2014;17:A241-A241.
3. Holden SE, Schernthaner G, Jenkins-Jones S, Currie CJ. Exogenous insulin and risk of all-cause mortality in type 2 diabetes: a dose-response association *Diabetologia* 2013;56:S96.

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Glossary of abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
ADOPT	A Diabetes Outcome Progression Trial
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation
ADA	American Diabetes Association
AGE	Advanced glycation end-product
aHR	Adjusted hazard ratio
AMP kinase	5' Adenosine Monophosphate-activated Protein kinase
ANOVA	Analysis of variance
ATP	Adenosine triphosphate
BMI	Body mass index
CADTH	Canadian Agency for Drugs and Technologies in Health
CI	Confidence interval
CPRD	Clinical Practice Research Datalink
DCCT	Diabetes Control and Complications Trial
DPP	Diabetes Prevention Program
DPP-4	Dipeptidylpeptidase-4
DIGAMI	Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction
EASD	European Association for the Study of Diabetes
EMA	European Medicines Agency
FDA	Food and Drugs Administration
FGS	First generation sulfonylurea

FPG	Fasting plasma glucose
GLINT	Glucose Lowering In Non-diabetic hyperglycaemia Trial
GLP-1	Glucagon-like peptide-1
GMS	General Medical Services
GOLD	GP online data
GP	General Practitioner
GPRD	General Practice Research Database
HbA_{1c}	Glycated haemoglobin
HDL	High-density lipoprotein
HES	Hospital Episode Statistics
HR	Hazard ratio
ICD	International Classification of Diseases
IDDM	Insulin Dependent Diabetes Mellitus
IDF	International Diabetes Federation
IFG	Impaired fasting glucose
IGF	Insulin-like Growth Factor
IGT	Impaired glucose tolerance
IQR	Interquartile range
IQWiG	Institute for Quality and Efficiency in Healthcare
ISAC	Independent Scientific Advisory Committee
LADA	Latent Autoimmune Diabetes of Adulthood
MACE	Major Adverse Cardiac Event
MH-OR	Mantel-Haenszel Odds Ratio
MINAP	Myocardial Ischaemia National Audit Project

MSGP4	4th National Study of Morbidity Statistics from General Practice
NHS	National Health Service
NIC	Net Ingredient Cost
NICE	National Institute for Health and Care Excellence
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NPH	Neutral protamine Hagedorn
ONS	Office for National Statistics
OR	Odds ratio
ORIGIN	Outcome Reduction with an Initial Glargine Intervention
PCA	Prescription Cost Analysis
QOF	Quality and Outcomes Framework
RCT	Randomised controlled trials
REACH	Reduction of Atherothrombosis for Continued Health
RR	Relative Risk
SD	Standard Deviation
SGLT2	Sodium-glucose co-transporter 2
SGS	Second generation sulfonylurea
SIGN	Scottish Intercollegiate Guidelines Network
SIR	Standardised incidence ratio
THIN	The Health Improvement Network
UGDP	University Group Diabetes Programme
UKPDS	United Kingdom Prospective Diabetes Study
VADT	Veterans Affairs Diabetes Trial
VAMP	Value Added Medicinal Products

WHO	World Health Organization

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1 Introduction

1.1. Background

1.1.1. Diabetes mellitus

Diabetes mellitus is a collection of metabolic disorders characterized by prolonged hyperglycaemia resulting from the reduced secretion of insulin, peripheral resistance to the action of insulin or a combination of the two. The different classes of diabetes mellitus, as defined by the American Diabetes Association are presented in Table 1.1.[1] Type 1 and type 2 diabetes were also formerly known as insulin dependent diabetes mellitus (IDDM) and non-insulin dependent diabetes mellitus (NIDDM), respectively. However, the use of these terms is no longer recommended as they can lead to the characterisation of diabetes by treatment type rather than the aetiology of the disease.

The World Health Organization (WHO) 1999 guidelines for the definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia recommend that diagnosis of diabetes should be based on fasting plasma glucose levels or the oral glucose tolerance test where venous plasma glucose levels are measured two hours after ingestion of a 75g oral glucose load (Table 1.2).[2] These recommendations were further updated in 2009 to allow the use of glycated haemoglobin (HbA_{1c}) as a diagnostic test for diabetes. A diagnosis of diabetes can be made if the HbA_{1c} level is ≥6.5% providing certain criteria are met: the use of stringent quality assurance tests, the use of assays standardised to criteria aligned to the international reference values (along with the recent introduction of the SI unit[3]) and also the absence of any conditions which prevent the accurate measurement of HbA_{1c} levels.[4] Unless symptoms of

hyperglycaemia are present or plasma glucose levels are unequivocally elevated, tests should be repeated on a separate day in order to confirm a diabetes diagnosis.[1,2]

Table 1.1 Aetiological classification of diabetes mellitus (abbreviated version of the American Diabetes Association (ADA) classification)[1]

Types of diabetes mellitus
1. Type 1 diabetes A. Immune mediated B. Idiopathic
2. Type 2 diabetes
3. Other specified types A. Genetic defects of beta-cell function B. Genetic defects in insulin action C. Diseases of the exocrine pancreas D. Endocrinopathies E. Drug or chemical induced F. Infections G. Uncommon forms of immune-mediated diabetes H. Other genetic syndromes sometimes associated with diabetes
4. Gestational diabetes mellitus

Table 1.2 WHO criteria for the diagnosis of diabetes and intermediate hyperglycaemia (1999 and 2011 guidelines)[2,4,5]

	Fasting glucose (mmol/l)		1hr glucose (mmol/l)		2hr glucose (mmol/l)		HbA_{1c} (% / mmol/mol
Normal	<6.1				<7.8 (implied)		-
IFG	≥6.1 and <7.0	and			<7.8 (if measured)		-
IGT	<7.0	and			≥7.8 and <11.1		-
Diabetes	≥7.0	or			≥11.1	or	≥6.5 / 47.5
Gestational diabetes	5.1–6.9	or	>10.0*	or	8.5–11.0		

* Although there are no established criteria for the diagnosis of diabetes based on the 1-hour post 75g oral glucose load.

Impaired glucose regulation (IGR, but also known as pre-diabetes or non-diabetic hyperglycaemia) occurs in people with glucose levels that are raised above normal but are lower than the diabetic range. Impaired glucose regulation may be referred to as impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) depending on whether the fasting glucose or plasma glucose levels following an oral glucose load are raised (Table 1.2). National Institute for Health and Care Excellence (NICE) guidelines recommend that patients with a fasting plasma glucose level of between 5.5 and 6.9mmol/l or a HbA_{1c} level of 6.0–6.4% (42–47mmol/mol) have a high risk of developing diabetes.[6] These patients should be offered an intensive lifestyle change programme with the aim of increasing physical activity, achieving and maintaining weight loss and modifying diet.[6] As these patients are at a higher risk of developing type 2 diabetes, they should also be monitored at least yearly.[6]

1.1.2. Type 2 diabetes

Type 2 diabetes is a chronic, progressive condition which results from either reduced insulin secretion, peripheral resistance to the action of insulin or both. Therefore, the condition differs from type 1 diabetes, which is characterised by the destruction of beta cells in the pancreas usually resulting in the complete failure of insulin production. In this regard, type 2 diabetes has been previously seen as a more mild form of diabetes. However, it is now clear that type 2 diabetes is associated with a risk of severe macrovascular and microvascular complications and requires complex clinical management.[7] Although type 2 diabetes is genetically determined, age of manifestation, its treatment requirements and its ultimate outcomes are largely related to obesity and physical inactivity.[8]

1.1.2.1. Prevalence and incidence of type 2 diabetes

In the UK, the overall prevalence of diabetes increased from 2.8% to 4.3% between 1996 and 2005.[9] In fact, the estimated number of people with diabetes in the UK has risen from 1.4 million to 2.9 million between 1996 and 2011 and an estimated 90% of these people have type 2 diabetes.[10] In 2012, there was an estimated 850,000 people with diabetes who were unaware of their condition or undiagnosed.[11] The prevalence of type 2 diabetes is predicted to increase to 5 million by 2025 if the current trend continues.[11]

Worldwide, it was estimated that 347 million people had diabetes in 2008.[12] In the US, the prevalence of diabetes is 8.3% and 90% to 95% of these people are likely to have type 2 diabetes.[13] Type 2 diabetes is the most common non-communicable disease globally with low and middle income countries now dealing with the greatest burden of diabetes.[14] Due to changes in life expectancy, diet and lifestyle, approximately 80% of people with diabetes live in low- to middle-income countries.[14]

Type 2 diabetes traditionally affected older people and used to be known as adult onset diabetes. However, the prevalence of type 2 diabetes in children and young adults is increasing due at least in part to obesity and sedentary lifestyle.[15,16]

As the early symptoms of type 2 diabetes can be mild, people with type 2 diabetes can remain undiagnosed for many years. In the US, it has been estimated that 25.8 million people had diabetes in 2010, where 18.8 million people had been diagnosed and 7.0 million people remained undiagnosed.[13] A study carried out in the US and Australia between 1978 and 1982, found that based on an estimate of the prevalence of retinopathy at diabetes diagnosis, the onset of type 2 diabetes is likely to be at least 4–7 years prior to clinical diagnosis.[17] It has been estimated that the proportion of people

with diabetes remaining undiagnosed or untreated in both developing and developed countries remains high and ranges from 24% of women in Scotland to 62% of men in Thailand.[18] Therefore, the true prevalence of diabetes may be even higher than estimated.

1.1.2.2. Aetiology of type 2 diabetes

Type 1 diabetes is an autoimmune endocrine disease which is often idiopathic but maternal factors, environmental factors and viruses may pay a role in the development of some cases.[14] The cause of type 2 diabetes has not been fully elucidated, however there are several predispositions and risk factors associated with the disease:

- Obesity
- Poor diet
- Lack of exercise
- Ageing
- Polygenic inheritance, family history and ethnicity
- High blood glucose during pregnancy affecting the unborn child

Obesity is perhaps the most significant modifiable risk factor for the development of type 2 diabetes. The mechanism by which obesity is related to type 2 diabetes is through the release of adipokines from the excess deposits of adipose tissue leading to the development of insulin resistance.[19] Data from National Health and Nutrition Examination Survey (NHANES) in the US has found that 85% of people with diabetes are overweight or obese and 55% of people are obese at diagnosis.[20] In addition, being overweight and particularly obese, especially at a younger age, is associated with an increased lifetime risk of diagnosed diabetes.[21] Hillier et al. demonstrated that there

was an inverse relationship between body mass index (BMI) and the age of onset of type 2 diabetes.[22] The Diabetes Prevention Program (DPP) found that intensive lifestyle intervention with a minimum of 7% weight loss and 150 minutes of physical activity per week is associated with a 58% reduction in diabetes incidence.[23] Physical activity may also have beneficial effects on insulin sensitivity.[24,25]

Type 2 diabetes also has a strong genetic basis where the concordance rates for type 2 diabetes were higher for monozygotic compared with dizygotic twins.[26] In addition, parental history of type 2 diabetes has also been shown to influence the distribution of body fat, energy expenditure, and insulin sensitivity in the offspring.[27] In the US, non-Hispanic whites have a lower prevalence of diabetes than Asian Americans, Hispanics, non-Hispanic blacks, American Indians and Alaska Natives.[28] In addition, the risk of developing type 2 diabetes is higher for Hispanics, Asians and Blacks compared with whites even after BMI is taken into account.[29] However, a recent study found that truncal obesity accounted for the two-fold excess incidence of type 2 diabetes observed in Indian Asian and Afro-Caribbean women but not men.[30] The reason for this increased risk in some ethnic groups has not been fully explained.

1.1.2.3. Symptoms of type 2 diabetes

Unlike type 1 diabetes, early symptoms of type 2 diabetes can be mild and type 2 diabetes can remain undiagnosed for many years, as people are not always aware that they have the condition. Type 2 often develops slowly over a period of years and symptoms of type 2 diabetes include:

- Polyuria
- Polydipsia

- Polyphagia
- Tiredness
- Unexplained weight loss and loss of muscle bulk
- Fungal infections e.g. thrush
- Slow healing cuts and wounds
- Blurred vision
- Cramps
- Constipation[31]

1.1.2.4. Natural history of type 2 diabetes

Type 2 diabetes is a chronic condition characterised by increasing insulin resistance in the early stages followed by progressive metabolic decompensation with the gradual deterioration in beta (β) cell function over time.[32] As type 2 diabetes progresses, treatment intensification from lifestyle interventions to one or more glucose-lowering therapies and eventually insulin is often required. The rate of progression varies between individuals and depends on multiple factors including, age, obesity and sedentary lifestyle.[32] Therefore patient education and commitment to make necessary lifestyle changes are important in order to modify the natural history of type 2 diabetes. Earlier identification of people with pre-diabetes could allow appropriate intervention at an early stage to prevent the development of type 2 diabetes.[33]

1.1.2.5. Long term complications of type 2 diabetes

People with type 2 diabetes are at risk of developing microvascular complications such as diabetic retinopathy, diabetic neuropathy, diabetic nephropathy and macrovascular complications including coronary artery disease, peripheral artery disease and stroke.[34] Type 2 diabetes is a progressive condition and its severity varies. People with type 2 diabetes may develop multiple complications, which may eventually lead to blindness, amputations, heart failure and stroke; whereas other people may develop no complications of diabetes within their lifetime. Diabetic retinopathy accounts for 1% of visual impairments and blindness.[35] People with diabetes have a markedly increased risk of lower limb amputation.[36] In addition, diabetes is the leading cause of renal failure[37] and is associated with more than a two-fold increased risk of stroke in those with elevated fasting plasma glucose levels.[38] In the WHO Multinational Study of Vascular Disease in Diabetes (WHO MSVDD), cardiovascular disease and renal disease accounted for 52% and 11% of deaths respectively in patients with type 2 diabetes.[39] Furthermore, in 2000, diabetes was attributed to 5.2% of all deaths and was the fifth leading cause of death worldwide.[40] Therefore, appropriate management of the condition, is vital in order to minimise the risk of developing microvascular and macrovascular complications.

1.1.2.6. Economic burden of type 2 diabetes

Type 2 diabetes places a significant economic burden on the National Health Service (NHS). In 2010–2011, the cost of type 2 diabetes in the UK was £8.8 billion in direct costs and £13 billion in indirect costs.[41] By 2035–2036, this is predicted to increase to £15.1 billion and £20.5 billion, respectively.[41] This represents an increase from 10% to

17% of total health resource expenditure.[41] In the financial year 2012–2013, 42.5 million prescription items for diabetes were dispensed in England with a net ingredient cost (NIC) of £764.1 million. This was an increase on the previous financial year against a background of a reduction in overall prescribing costs.[42] The global health expenditure for diabetes in people aged 20–79 years has been predicted to increase to $490 billion in 2030.[43]

1.1.2.7. Management of type 2 diabetes

1.1.2.7.1. Aims of treatment

The management of type 2 diabetes can be complex. The aim of treatment is to reduce disease progression, increase quality of life, reduce the symptoms of diabetes, reduce the risk of developing microvascular and macrovascular complications, increase life expectancy, and minimise the risk of unwanted or harmful side effects. Adequate control of blood glucose remains a primary goal in the management of type 2 diabetes. Lifestyle interventions including the provision of advice on diet, exercise, weight loss and smoking cessation play an important role. Many people with type 2 diabetes progress to glucose-lowering therapies including insulin when lifestyle interventions have failed to provide adequate blood glucose control.

Minimising cardiovascular risk factors including the use of blood pressure and cholesterol lowering interventions where indicated also play a role in the management of type 2 diabetes. A previous study has shown that people with diabetes and no history of myocardial infarction have as high a risk of myocardial infarction as those patients without diabetes but with a history of myocardial infarction.[44] In the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in

Primary Care (ADDITION-Europe) multicentre, randomised control trial (RCT), intensive management of risk factors (HbA_{1c}, cholesterol and blood pressure) in people who had screened positive for type 2 diabetes resulted in a non-significant reduction in the composite endpoint (cardiovascular death, cardiovascular morbidity, revascularisation and non-traumatic amputation, hazard ratio (HR) 0.83, 95% CI 0.65–1.05) when compared with routine diabetes care.[45] Tight blood pressure control has also been shown to reduce the risk of diabetes related death, stroke and the progression of retinopathy in people with type 2 diabetes.[46] Blood pressure targets of less than 140/80mmHg are recommended for most people with diabetes, with a target of less than 130/80mmHg recommended for people with type 2 diabetes and kidney, eye, or cerebrovascular disease.[47] Statins should be considered for all patients with type 2 diabetes over the age of 40 and also in those under the age of 40 who have signs of target-organ damage, HbA_{1c} level of greater than 9%, low high-density lipoprotein (HDL) cholesterol and raised triglyceride concentration, hypertension, or a family history of premature cardiovascular disease.[47] However, aspirin is now only recommended for secondary prevention in people with established cardiovascular disease.[47]

1.1.2.7.2. Available glucose-lowering therapies

Treatment options begin with diet modification and lifestyle interventions but often glucose-lowering agents are required.[47] Glucose-lowering therapies currently available in the UK are listed in **Table 1.3**.[47] People with type 1 diabetes require insulin from onset, whereas those with type 2 diabetes are likely to be switched to insulin later in the natural history of their disease.[47]

Table 1.3 Glucose-lowering therapies available in the UK

Class of glucose-lowering therapies	Examples
Insulin	Animal insulin
	Human insulin
	Analogue insulin
Sulfonylureas	Glibenclamide
	Gliclazide
	Glimepiride
	Glipizide
	Tolbutamide
Biguanide	Metformin
Intestinal alpha-glucosidase inhibitor	Acarbose
Meglitinides	Nateglinide
	Repaglinide
Thiazolidinediones	Pioglitazone
Dipeptylpeptidase-4 (DPP-4) inhibitors	Linagliptin
	Saxagliptin
	Sitagliptin
	Vildagliptin
Glucagon-like peptide-1 (GLP-1) agonists	Exenatide
	Liraglutide
	Lixisenatide
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	Dapagliflozin

1.1.3. Insulin use in type 2 diabetes

1.1.3.1. The role of insulin in the regulation of blood glucose

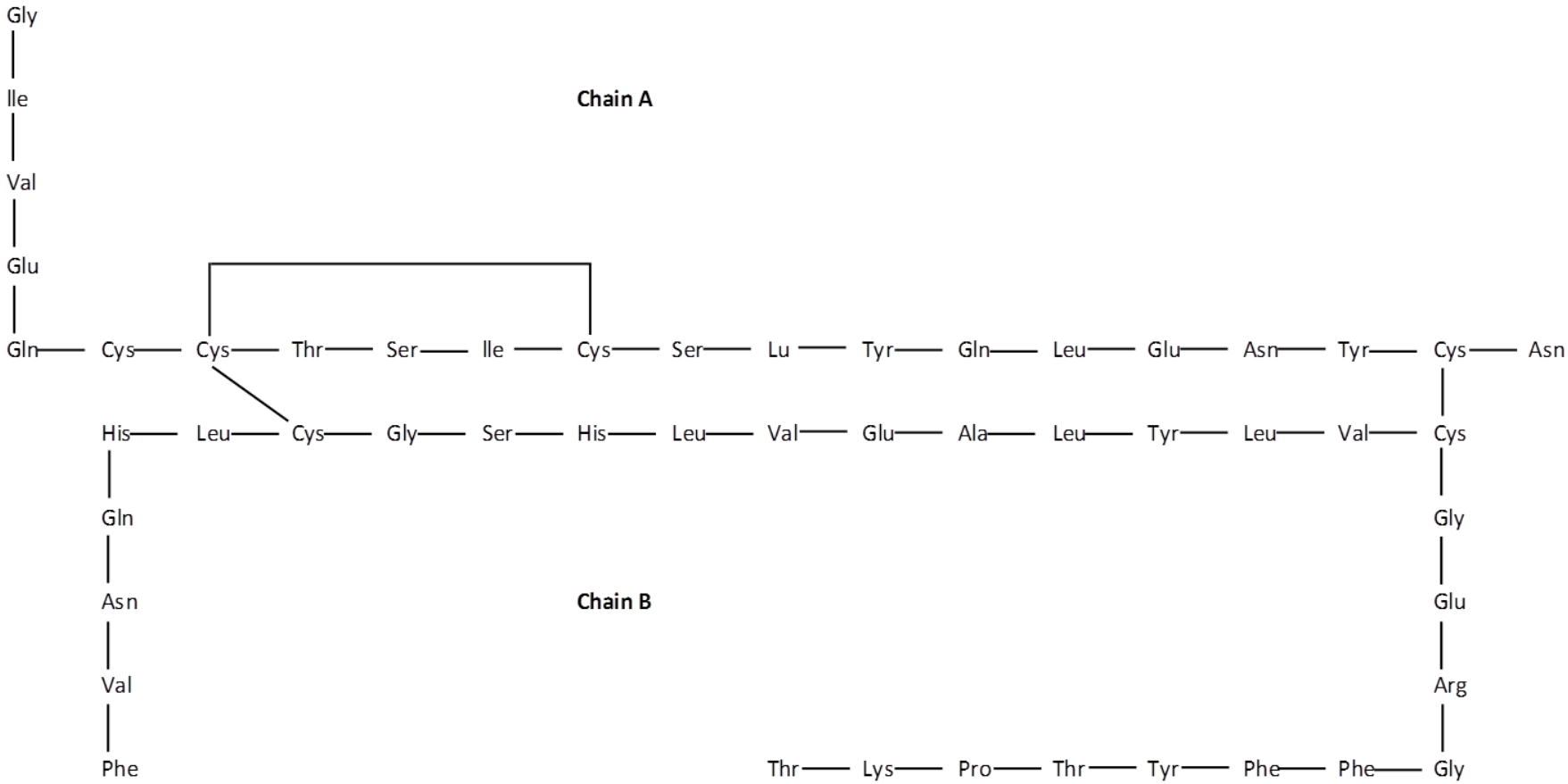
Insulin is a 51 amino acid peptide hormone (Figure 1.1)[48] produced by beta cells in the islets of Langerhans in the pancreas. Insulin secretion is primarily influenced by glucose but can also be influenced by amino acids, gastrointestinal peptides (e.g. glucagon-like peptide 1) and neurotransmitters. The glucose transporter 2 (GLUT2 transporter) transfers glucose into pancreatic beta cells where it is phosphorylated into glucose-6-phosphate by the glucokinase enzyme.[49] Glucose-6-phosphate is then converted to adenosine triphosphate (ATP), which then inhibits ATP sensitive potassium channels to cause depolarisation of the beta cell membrane.[49] This in turn causes voltage-gated calcium channels to open and insulin to be released.[49]

Insulin primarily acts in the liver, skeletal muscle and adipose tissue. Insulin lowers blood glucose through the following metabolic effects:

- Inhibition of gluconeogenesis in the liver and kidney. Protein breakdown and lipolysis of stored triglycerides is inhibited and protein synthesis is promoted.
- Inhibition of glycogenolysis through the inhibition of glycogen phosphorylase and the stimulation of glycogen synthase.
- Increased glucose uptake into adipocytes and skeletal muscle cells.
- Increased glucose breakdown (glycolysis) in adipocytes and skeletal muscle cells.[49]

In addition, insulin reduces the secretion of glucagon, a peptide hormone secreted by the alpha cells located at the periphery of the islets in the pancreas. Glucagon has the opposite effect of insulin in that it stimulates gluconeogenesis and glycogenolysis in the liver and kidney.[49]

Figure 1.1 Chemical structure of human insulin, adapted from Sweetman et al (2014)



1.1.3.2. History of insulin as a treatment for diabetes

Insulin is the oldest medicine with the largest potential to lower blood glucose. Insulin was first administered by Banting to Leonard Thompson in 1922.[50] However, the product was crude and no noticeable clinical benefit was received. Collip purified the extract, which when injected, produced clinical benefit.[50] By 1926, Abel had further improved the purity of insulin but this led to faster absorption and clearance from the body.[51] To increase the duration of action of insulin, Hagedorn added an alkaline protein (protamine) to insulin which made it less soluble at neutral pH.[51,52] Ten years later, Nordisk produced insulin isophane or neutral protamine Hagedorn (NPH) insulin by mixing soluble insulin with protein in precisely balanced proportions.[51] The duration of action of insulin was prolonged further through the addition of zinc to soluble insulin.[51]

Early preparations of insulin were associated with a risk of allergic reactions at the injection site due to the presence of residual impurities in the preparation.[51] Clean insulins were produced through a process of multiple recrystallization (e.g. new monocomponent (Novo), highly purified (Nordisk) and single peak (Lilly) pork insulins). This meant that the development of lipodystrophies could be avoided.[51]

Insulin became the first protein to be chemically sequenced (in 1955) and chemically synthesised (in 1963).[53] However, it was not until 1978 that synthetic human insulin could be mass produced through recombinant DNA technology.[53] In 1983, Lilly launched the first biosynthetic human insulin.[51] By altering the structure of insulin, improvements in the onset and duration of action of insulin were made. This lead to the development of several rapid-acting e.g. (insulin lispro and insulin aspart) and long-acting analogue insulins (e.g. insulin glargine, insulin detemir).[51]

1.1.3.3. Types of insulin available

Insulin is available in short, intermediate and long-acting form (Table 1.4).

Table 1.4 Types of insulin available in the UK

Duration of action	Type	Drug Name
Short-acting	Human	Insulin (soluble/neutral)
	Analogue	Insulin aspart
		Insulin lispro
		Insulin glulisine
Intermediate and long-acting	Human	Insulin zinc suspension
		Isophane (or NPH) insulin
		Protamine zinc insulin
	Analogue	Insulin degludec
		Insulin detemir
		Insulin glargine
Biphasic	Human	Biphasic insulin isophane
	Analogue	Biphasic insulin aspart
		Biphasic insulin lispro

1.1.3.3.1. Prescribing guidelines for type 2 diabetes

Insulin is recommended by the NICE as third line therapy for the management of type 2 diabetes when metformin plus sulfonylurea (where indicated) are not sufficient to maintain a HbA_{1c} level below 7.5%.[54] Other options at the same point in the treatment pathway include thiazolidinediones or exenatide but it is recommended that patients are subsequently switched to insulin plus metformin and a sulfonylurea if HbA_{1c}

remains above 7.5%.[54] The addition of insulin is also recommended for those patients who have followed alternative treatment pathways and combinations of metformin or sulfonylurea plus a DPP-4 inhibitor or a thiazolidinedione are insufficient to maintain a HbA_{1c} level of less than 7.5%.[55]

Scottish Intercollegiate Guidelines Network (SIGN) recommend metformin as first-line therapy for type 2 diabetes.[56] As an alternative, a sulfonylurea can be prescribed if the patient has an intolerance to metformin or exhibits osmotic symptoms or weight loss.[56] The preferred second-line option is the addition of a sulfonylurea.[56] Alternatively a thiazolidinedione or DPP-4 inhibitor can be prescribed.[56] GLP-1 receptor agonists or insulin can be used in combination with metformin or sulfonylurea if tolerated as third line options.[56] The SIGN guidelines recommend that HbA_{1c} levels should be maintained below 7% with the introduction of individualized targets where appropriate to balance potential benefits with harms, for example hypoglycaemia and weight gain.[56]

ADA and European Association for Study of Diabetes (EASD) guidelines, recommend metformin first line where no contraindications exist.[7] As second line therapy, the addition of a sulfonylurea, thiazolidinedione, DPP-4 inhibitor, GLP-1 receptor agonist or basal insulin to existing metformin therapy is recommended.[7] However, at this stage, the EASD and ADA advocate a patient-centred approach to selecting which glucose-lowering medication is appropriate to achieve adequate glucose control while minimising side effects.[7] As third-line therapy, the ADA and EASD guidelines recommend using three or more glucose-lowering agents in combination and this can include insulin.[7] In fact, it suggests that insulin may be the most effective choice for achieving target glucose levels especially when HbA_{1c} is very high (≥9.0%).[7] The

ADA/EASD guidelines recommend a HbA_{1c} target of <7% for most people with type 2 diabetes.[7] However, in those people newly diagnosed, with no significant coexisting cardiovascular disease and long life expectancy, a HbA_{1c} level of <6.5% may be appropriate providing it can be achieved without causing other significant side effects such as hypoglycaemia.[7] Conversely, in those people with a history of severe hypoglycaemia, limited life expectancy, extensive comorbid conditions, or an inability to achieve a lower target glucose despite intensive management, a higher HbA_{1c} target of less than 7.5–8% may be appropriate.[7]

The International Diabetes Federation (IDF) recommends that insulin should be used as an option third line when a combination of metformin (where indicated) and one other glucose-lowering medication has failed to adequately control blood glucose (recommended HbA_{1c} target of <7%).[57]

1.1.3.4. Epidemiology of insulin use

The number of people using insulin for type 2 diabetes in the UK is not known. However, the cost of insulin has increased year on year.[42] For the financial year 2005/6, the NIC of insulin for the NHS in England was £220.8 million.[42] By 2012/13, this had increased to £320.0 million.[42] This could be due in part to the use of more expensive insulin analogues. However, the number of prescription items for insulin also increased from 4.7 million to 6.2 million during the same period.[42]

In the US, the 2007-2009 National Health Interview Survey found that 26% of people in the US with diagnosed diabetes were treated with insulin (12% receiving insulin monotherapy and 14% receiving insulin in combination with oral glucose-lowering medication).[13]

1.2. Thesis rationale

In 2014, an estimated 6.2% of adults had diabetes.[58] Although the cause of type 2 diabetes is multi-factorial, it is largely related to obesity and physical inactivity,[8] both of which are potentially modifiable risk factors. Life expectancy of people diagnosed with type 2 diabetes at the age of 50 is thought to be reduced by 6 years when compared to a counterpart without diabetes.[59] Type 2 diabetes is associated with a risk of severe macrovascular and microvascular complications and diabetes currently accounts for 10% of total health resource expenditure in the UK.[41] Type 2 diabetes requires complex clinical management in order to reduce the risk of developing complications.[7] As such it is important to have an understanding of the epidemiology of the condition and the risks and benefits associated with glucose-lowering therapies used to manage hyperglycaemia in type 2 diabetes. Insulin, a commonly prescribed glucose-lowering therapy, has been associated with an increased risk of cardiovascular events, cancer and all-cause mortality in comparison with other glucose-lowering therapies in some epidemiological studies[60–62] and this finding warrants further investigation.

In order to characterise the epidemiology of type 2 diabetes and to investigate the prevalence, costs, risks and benefits of using insulin in type 2 diabetes, six studies were carried out and the specific rationale for each is outlined below.

1.2.1. Incidence of type 2 diabetes

Between 1993 and 2010, the proportion of the UK population who were estimated to be obese increased from 13% to 26% for men and 16% to 26% for women.[63] For children, the prevalence of obesity has increased between 1995 and 2010 from 11% to

17% and from 12% to 15% for boys and girls, respectively.[63] Masso Gonzalez and colleagues reported an increase in the incidence of type 2 diabetes increased from 2.60 (95% CI 2.47–2.74) per 1000 person-years in 1996 to 4.31 (4.21–4.42) per 1000 person-years in 2005.[9] However, to our knowledge there are no further up to date estimates of the incidence of type 2 diabetes in the UK.

We hypothesised that between 1991 and 2010, the diagnosed incidence of type 2 diabetes had increased and during the same period there had been an increase in the proportion of people diagnosed at a younger age.

1.2.2. Prevalence of type 2 diabetes

The worldwide prevalence of diabetes has been estimated as 8.3% and 382 million people have been estimated to have diabetes.[43] Figures published using data from the Quality and Outcomes Framework (QOF) have reported an increase in the number of people with diagnosed diabetes in the UK from 1.4 million in 1996 to 3.2 million in 2013.[64] Masso Gonzalez and colleagues reported an increase in the prevalence of diagnosed type 2 diabetes from 2.47% in 1996 to 3.9% in 2005.[9] However, to our knowledge, there are no up to date estimates of the UK prevalence of type 2 diabetes specifically.

People with type 2 diabetes are at risk of developing microvascular and macrovascular complications, and have at least twice the risk of death as people without diabetes.[40] In 2005, 11.6% of deaths in people aged 20–79 in England were attributed to diabetes.[65] However, improvements in survival have also been reported.[66] The publication of the NICE guidelines[54] and findings from the United Kingdom Prospective Diabetes Study (UKPDS)[67], the introduction of QOF[68] and the launch of glucose-

lowering therapies with novel modes of action[69] may have had an impact on glycaemic control in this population.

We hypothesised that between 1991 and 2013, the prevalence of type 2 diabetes increased in the UK. Furthermore, we hypothesised that, during the same period, the survival of people type 2 diabetes had improved due to improved diabetes management. Following on from the previous study, improved survival and increased incidence would explain, at least in part, any increase in the prevalence of type 2 diabetes observed.

1.2.3. Incremental cost of analogue insulin

In the UK, NICE has recommended insulin glargine and rapid-acting insulin analogues as an option for patients with type 1 diabetes but has stated that long-acting insulin analogues should only be used in type 2 diabetes patients in specific circumstances.[55,70] A Cochrane review comparing long-acting insulin analogues with NPH insulin in type 2 diabetes patients concluded that there was no evidence of a beneficial effect in terms of glycemic control and only a minor benefit in terms of a reduction in symptomatic nocturnal hypoglycemic events.[71] Despite this, successful marketing, the withdrawal of some human insulin products as insulin manufacturers focus on their newer patentable products[72] and the improved pharmacokinetic profile of insulin analogues[71,73] may have contributed to a steady increase in the use of insulin analogues since the launch of insulin lispro in 1996.[69]

We hypothesised that the volume of insulin analogues prescribed in the UK has increased since their introduction. Due to the increased unit cost of insulin analogues

in comparison with their human insulin alternatives, we hypothesised that this would be associated with a high incremental cost to the NHS.

1.2.4. Prevalence of type 2 diabetes treated with insulin

An increase in the prevalence of diabetes[9] is likely to lead to a corresponding increase in the prevalence of type 2 diabetes treated with insulin. The number of insulin items dispensed on NHS prescriptions in England has increased year on year.[42] However, the number of people with type 2 diabetes treated with insulin in the UK is not known. The publication of the findings from UKPDS and the introduction of QOF may have encouraged and incentivised the initiation of insulin in people with type 2 diabetes in order to achieve tighter glycaemic control. The introduction of insulin analogues may have also overcome some of the barriers to insulin initiation, which can include both treatment complexity and fear of inducing hypoglycaemia.[74] In the US, between 2007–2009, 26% of patients with diabetes were using insulin, 58% were using oral glucose-lowering agents and 16% were diet-controlled only.[13] However, the number of people with type 2 diabetes treated with insulin in the UK is unknown.

We hypothesised that the prevalence of people with type 2 diabetes treated with insulin in the UK had increased between 1991 and 2010 with a corresponding increase in the proportion of patients with type 2 diabetes treated with insulin during the same period.

1.2.5. The use of insulin in type 2 diabetes

Insulin has an unlimited potential to lower blood glucose and is a well-established treatment for type 2 diabetes. ADA and EASD guidelines recommend a patient-centred approach with the aim of achieving adequate glucose control while minimising side effects. Two common side effects associated with insulin injections are weight gain and hypoglycaemia. Weight gain is associated with an increased risk of cardiovascular disease and should be minimised in type 2 diabetes. Two recent review articles, have described how both insulin and hypoglycaemia may have vascular effects which are thought to be greatest in people with pre-existing cardiovascular disease and diabetes.[75,76] In addition, as a growth factor, insulin may affect cancer progression.[77] However, this is a complex area where high glucose levels have also been linked to increased cancer risk.[78]

Some epidemiological studies have shown that the use of insulin is associated with an increased risk of cardiovascular events, cancer and all-cause mortality in comparison with other glucose-lowering therapies.[60–62] In contrast, large RCTs such as Action to Control Cardiovascular Risk in Diabetes (ACCORD) have found no adverse safety signals associated with the use of insulin.[79] However, these studies were designed to assess the benefits of intensive glucose control rather than the safety of insulin itself. The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial demonstrated that insulin glargine had no statistically significant impact on cardiovascular outcomes and cancers compared with standard treatment.[80] However, subjects could receive multiple glucose-lowering therapies making individual comparisons difficult.

The findings from epidemiological studies suggest that further investigation into the role of both hyperinsulinaemia and exogenous insulin in type 2 diabetes is warranted

in order to determine how insulin should be used in people with type 2 diabetes. Any potential risks associated with insulin therapy need to be seen within the context of its glucose-lowering potential, where insulin is often ultimately required for the achievement of adequate glucose control due to the progressive loss of beta cell function over time.[7] However, there is a shortage of RCTs examining the risks and benefits of using insulin on long term clinical outcomes such as cardiovascular events, cancer and death from all causes. In the absence of well-designed RCTs, there is an opportunity for large-scale observational studies to investigate the safety of insulin in people with type 2 diabetes. However such studies should be designed in such a way as to minimise the risk of confounding. As stated in section 1.2., we hypothesise that insulin is a commonly prescribed medicine in type 2 diabetes. Therefore, any concern surrounding the safety of insulin in type 2 diabetes could represent a major public health issue.

We hypothesised that the increasing insulin dose in type 2 diabetes would be associated with an increased risk of all-cause mortality, major adverse cardiac events (MACE) and cancer in people with type 2 diabetes.

1.2.6. The use of metformin in combination with insulin in type 2 diabetes

When used in combination, metformin may attenuate any risks associated with insulin. Metformin may further protect against cancer through additional AMP kinase dependent and independent effects.[81] In addition, results from UKPDS showed that metformin reduced the risk of all-cause mortality, diabetes-related mortality and myocardial infarction versus standard care even though patients in the metformin arm had a mean HbA1c of 0.6% lower than standard care.[82] When used in conjunction with

insulin, metformin has been associated with similar glucose control, but lower insulin doses and less weight gain.[83] In addition, relative to the use of insulin alone, the use of metformin in combination with insulin has been associated with a reduced risk of cardiovascular events, cancer and death from any cause.[61] However, this study did not account for insulin dose.

We hypothesised that the use of metformin in combination with insulin in people with type 2 diabetes would be associated with a reduced risk of all-cause mortality, MACE and cancer versus the use of insulin alone after adjusting for insulin dose.

1.3. Aims and objectives

The aim of this thesis is to undertake a series of retrospective, cohort studies to characterise the epidemiology of type 2 diabetes and insulin use and to investigate the costs, risks and benefits of using insulin in type 2 diabetes using Clinical Practice Research Datalink (CPRD). Specifically, the objectives and structure of this thesis are described in Table 1.5.

Each of the thesis objectives will be addressed by a separate chapter of the thesis (Chapters 4–10). Chapters 4–10 will all start with an introduction summarising the existing literature on the given topic. This will be followed by a section providing detailed methods for the specific study. Results are then presented, followed by a discussion of the study findings and a comparison with existing literature.

Table 1.5 Thesis objectives

Chapter number	Objective
Chapter 2	To outline the current available evidence on the use of insulin in type 2 diabetes.
Chapter 3	To provide an overview of the methods and data sources used for the series of studies described in chapters 4–10.
Chapter 4	To characterise the incidence of type 2 diabetes between 1991 and 2010 and to determine if the proportion of people diagnosed by the age of 40 has increased.
Chapter 5	To estimate the prevalence of type 2 diabetes in the UK between 1991 and 2010.
Chapter 6	To estimate the prevalence and number of people using insulin in the UK between 1991 and 2010 by diabetes type.
Chapter 7	To calculate the annual NHS spend on insulin in the UK between 2000 and 2009 and to calculate the incremental cost to the NHS of prescribing analogue insulin preparations instead of human insulin.
Chapter 8	To evaluate if there is an association between insulin dose and all-cause mortality, incident major adverse cardiovascular events (MACE), and incident cancer.
Chapter 9	To determine if there is an association between insulin dose and all-cause mortality and other serious events in people with type 2 diabetes treated with insulin plus metformin and to determine if concomitant metformin with insulin reduces the risk of adverse events versus insulin monotherapy.
Chapter 10	To discuss the main findings of the series of retrospective studies and their clinical and public health implications.

2. Literature review

Insulin is an established glucose-lowering therapy and there is long-term clinical experience of the use of this therapy for the management of hyperglycaemia in diabetes. Type 1 diabetes is characterised by the destruction of beta cells in the pancreas usually resulting in the complete failure of insulin production. Therefore, insulin therapy is essential for all people with type 1 diabetes. Although the goal of reducing microvascular and macrovascular complications remains the same, type 2 diabetes differs from type 1 diabetes as it is characterised by early insulin resistance and insulin remains one of an armoury of potential glucose lowering medications and lifestyle interventions. However, many patients with type 2 diabetes will progress to insulin, due in part to the progressive loss of beta-cell function over time.[84] The aim of this chapter is to review the current evidence on the risks and benefits of using exogenous insulin in type 2 diabetes on these serious adverse outcomes.

2.1. Complications of diabetes

2.1.1. Macrovascular complications

The association between diabetes and cardiovascular disease was demonstrated in the Framingham study.[85] The mechanisms linking type 2 diabetes and macrovascular disease are complex and multifactorial. Type 2 diabetes is characterised by varying degrees of insulin deficiency and insulin resistance leading to hyperglycaemia, which can predispose people with type 2 diabetes to developing atherosclerosis. Atherosclerosis can develop in type 2 diabetes following chronic inflammation and endothelial injury.[34] Oxidative stress plays an important role in the development of

diabetic complications including cardiovascular disease.[86] Hyperglycaemia may cause vascular damage via several mechanisms including: increased polyol pathway flux, increased formation of advanced glycation end-products (AGEs), protein kinase C activation, increased flux through the hexosamine pathway, formation of oxidized lipids via the cyclooxygenase and lipoxygenase pathways.[87,88] The 'common soil' hypothesis postulates that diabetes and cardiovascular disease share underlying causes.[89] A period of insulin resistance and hyperinsulinaemia precedes the development of type 2 diabetes.[90] Insulin resistance is a risk factor for cardiovascular disease[91,92] and insulin resistance has been shown to be a predictor of cardiovascular risk in people without diabetes.[91] Therefore, insulin resistance promotes the development of atherosclerosis even in the absence of hyperglycaemia. Consequently, macrovascular complications can precede the onset of diabetes and can often be present at the time of diabetes diagnosis.[90] Type 2 diabetes typically develops within the setting of metabolic syndrome, abdominal obesity, hypertension, hyperlipidaemia and increased coagubility.[34] These are also risk factors for the development of cardiovascular disease.[34] Furthermore, type 2 diabetes, insulin resistance and hyperglycaemia may have an effect on fibrinolysis and platelet hyperreactivity.[93,94]

Cardiovascular disease is the cause of death for 50% of people with type 2 diabetes.[95] People with metabolic syndrome are at a two-fold increased risk of developing cardiovascular disease and a five-fold greater risk of developing type 2 diabetes.[90] Haffner and colleagues reported that the risk of myocardial infarction was similar for people with diabetes and people without diabetes but with a prior history of myocardial infarction.[44] Conversely, other studies have reported contradictory results. A meta-analysis by Bulugahapitiya and colleagues reported that patients with diabetes and no history of myocardial infarction had a 43% lower risk of coronary heart disease

events when compared with people with a previous history of myocardial infarction but no diabetes (summary odds ratio 0.56, 95% CI 0.53–0.60).[96] Echouffo-Tcheugui and colleagues have therefore suggested that CVD risk in people with type 2 diabetes may not always be as high as for CVD survivors who do not have diabetes.[97]

It has been reported that people with diabetes have more than a two-fold increased risk of death due to vascular causes compared with people without diabetes (2.32, 95% CI 2.11–2.56, following adjustment for age, sex smoking status and BMI).[59] People with type 2 diabetes are also at increased risk of mortality following a myocardial infarction.[98,99] This has been shown to be particularly the case for women.[98,99] In addition, the risk of stroke is higher in people with type 2 diabetes compared with no diabetes.[100–103] Microvascular disease has been found to be an independent risk factor for the development of cardiovascular disease.[104]

2.1.2. Microvascular complications

People with type 2 diabetes are at risk of developing microvascular complications including neuropathy, nephropathy and retinopathy. Several mechanisms have been reported to link hyperglycaemia and type 2 diabetes with the development of diabetic retinopathy including osmotic stress due to sorbitol accumulation, formation of AGEs, oxidative stress and growth factors such as vascular endothelial growth factor (VEGF), growth hormone and transforming growth factor.[34,105] Retinopathy is thought to develop up to seven years prior to the diagnosis of type 2 diabetes.[17]

The mechanism of the development of diabetic nephropathy may contain all or some of the pathways described for the development of diabetic retinopathy.[34] During the development of diabetic nephropathy, possible changes to the kidney include

increased glomerular basement membrane thickness, microaneurysm formation and mesangial nodule formation.[34] Up to 7% of people with type 2 diabetes will have microalbuminuria at diagnosis.[106] In the UK, type 2 diabetes is the leading cause of end stage kidney failure.[11] Diabetic nephropathy is the most common cause of renal failure in the US and accounts for up to 44% of new cases.[107] In the UKPDS, the prevalence of microalbuminuria, macroalbuminuria and elevated plasma creatinine or renal replacement therapy was 24.9%, 5.3% and 0.8%, respectively, 10 years following diagnosis of type 2 diabetes.[108]

The development of diabetic neuropathy is not completely understood but possible mechanisms may include polyol accumulation, injury from AGEs and oxidative stress.[34] Diabetic peripheral neuropathy has been estimated to affect at least 20% of adults with diabetes.[109]

Hyperglycaemia has been shown to be a risk factor for the development of microvascular complications in observational studies.[110] In a Cochrane systematic review, intensive control of blood glucose reduced the risk of a composite outcome of microvascular diseases (relative risk (RR) 0.88, 95% CI 0.82–0.95), nephropathy (0.75, 0.59-0.95), retinopathy (0.79, 0.68-0.92) and retinal photocoagulation (0.77, 0.61 to 0.97) when compared with standard blood glucose control.[111] In a systematic review and meta-analysis undertaken by Coca and colleagues, intensive control of blood glucose was associated with a significant reduction in the risk of micro- and macroalbuminuria but no significant reduction in the risk of end stage renal disease. However, the number of events was small. Following the 10-year follow-up to UKPDS, a reduction in the risk of microvascular disease (RR 24%, p=0.001) was observed despite the loss in the between-group difference in HbA_{1c} after 1 year.[112]

2.1.3. Cancer

Worldwide, it has been estimated that 384 million people have diabetes and 33 million people are living with cancer.[14,113] In 2012, there were 14.1 million new cases of cancer and 8.2 million deaths related to cancer.[113] The latest IDF figures indicate that the worldwide prevalence of diabetes in adults is 8.3%, and the number of people living with diabetes is predicted to increase to 592 million within the next 25 years.[14] As both diabetes and cancer are common conditions there is considerable potential for overlap, with people with diabetes also developing cancer and vice versa. However, people with diabetes may also be at increased risk of developing cancer compared with the general population.[84]

The association between diabetes and cancer can be partly explained by metabolic derangements that are related to diabetes, such as hyperglycaemia, insulin resistance, hyperinsulinaemia and oxidative stress.[84,114,115] In type 2 diabetes, insulin resistance can cause hyperglycaemia, leading to increased secretion of insulin from the pancreas. This results in hyperinsulinaemia, which has been linked to tumour development.[19] Insulin is a growth factor with metabolic and mitogenic (cell proliferating) effects mediated through the insulin/insulin-like growth factor (IGF) axis.[114] Insulin can bind to insulin receptors leading to antiapoptotic actions and mitogenesis.[84] In addition, insulin may be associated with tumour development through a decrease in insulin like growth factor binding protein (IGFBP-1 and possibly IGFBP-2), leading to increased IGF-1 bioavailability.[84] IGF-1 is known to have proliferative and anti-apoptotic actions on target cells and has more potent mitogenic effects relative to insulin.[84] IGF-1 and insulin receptors are expressed on most cancer cells.[84] Therefore, insulin and IGF-1

have broad effects and cancer cells remain responsive to insulin, particularly in the presence of hyperinsulinaemia.[19]

Hyperinsulinaemia may cause a decrease in the production and blood level of sex hormone binding globulin leading to an increase in testosterone levels in females and an increase in the circulating levels of oestrogen in both genders.[84,116] Increasing levels of sex hormones have been linked to an increase in the risk of endometrial and postmenopausal breast cancer.[84] Conversely, free and total testosterone levels may be lower in men with diabetes compared to those without diabetes and this may explain the lack of association between diabetes and prostate cancer.[116] However, testosterone levels have not been consistently linked to prostate cancer risk.[84]

It has been proposed that hyperglycaemia may facilitate the proliferation of cancer cells as cancer cells rely on aerobic glycolysis in order to generate energy and therefore have a high glucose requirement – the Warburg effect.[117] However, hyperglycaemia is thought to play a less important role in the development of cancer in comparison with hyperinsulinaemia and cancer cells have been shown to consume high levels of glucose regardless of plasma glucose levels.[118] A meta-analysis, which combined the results of four RCTs, did not find an association between improved glucose control and a lowering of cancer risk.[119]

Obesity, the metabolic syndrome and diabetes are thought to precipitate chronic oxidative stress and inflammation. Oxidative stress is an imbalance between tissue oxidants including reactive oxygen species (ROS), free radicals and antioxidants which can cause cellular damage and may play a role in the development of cancer.[115]

The association between diabetes and cancer may also be explained by the shared risk factors associated with the two diseases—for example, ageing, gender, obesity, diet,

physical inactivity and socioeconomic status.[84,114,115] In economically developed countries, 78% of all newly diagnosed cancers occur in people over the age of 55 years.[13] The prevalence of type 2 diabetes also increases with increasing age.[13] With the exception of the sex-specific cancers, males have a higher incidence of both diabetes and cancer.[84]

Obesity is a risk factor for the development of both type 2 diabetes and cancer.[120] Excess deposits of adipose tissue release more adipokines, which can lead to insulin resistance and progression to type 2 diabetes.[19,116] Obesity is also linked to the development of cancer due to an increase in the circulating levels of sex hormones.[19] In addition, as a state of chronic inflammation, obesity may affect the progression of cancer through the production of pro-inflammatory cytokines such as interleukin-6 and tumour necrosis factor-α in adipose tissue.[84,115] The DPP found that weight loss and physical activity reduced the risk of diabetes in high risk people by 58%.[121] People who are overweight (BMI≥25 and <30kg/m^2) or obese (BMI ≥31kg/m^2) are at an increased risk of a range of malignancies including cancers of the colon, liver, breast, endometrium, gallbladder, kidney, pancreas, and oesophagus.[116]

The strength of the relationship between diabetes and cancer is likely to depend on cancer site.[120] Several meta-analyses have combined the results of studies investigating the association between diabetes and cancer. Meta-analyses have demonstrated an increased risk of breast cancer in women with diabetes[122,123] and type 2 diabetes specifically.[123,124] A significant increase in the risk of colorectal cancer in people with diabetes has also been demonstrated in several meta-analyses.[125–129] However, Luo et al did not find a clear association between the duration of diabetes and the incidence of colorectal cancer.[128] Larsson and colleagues combined the results

of 16 case-control and cohort studies and reported an association between diabetes and an increased risk of bladder cancer (1.24, 1.08–1.42).[130] In a separate meta-analysis, an association between diabetes and kidney cancer was demonstrated but there was heterogeneity between the included studies (RR 1.42, 1.06–1.91).[131] Other meta-analyses have found an association between diabetes and endometrial cancer, (RR 2.10, 95% CI 1.75–2.53),[132] non-Hodgkin's lymphoma (1.22 95% CI 1.07- 1.39),[133] leukaemia (1.22, 95% CI 1.03-1.44),[133] and hepatocellular carcinoma.[134–136] An non-significant association between type 2 diabetes and an increased risk of non-Hodgkin's lymphoma was reported in a meta-analysis by Chao and colleagues, but they also reported methodological weakness in the included studies.[137] A recent meta-analysis has demonstrated that diabetes is associated with a reduced risk of prostate cancer.[138] The studies included in all these meta-analyses were mainly observational in nature.

Insulin is produced in the beta cells of the pancreas and transported to the liver via the hepatic portal vein. Therefore these organs have the highest exposure to endogenous insulin.[84] Diabetes-related steatosis, non-alcoholic fatty liver disease and cirrhosis may also increase the risk of developing liver cancer.[84] The relationship between diabetes and cancer may be further complicated by reverse causality where pancreatic cancer can cause abnormal production of glucose. Carstensen and colleagues found that the relative risk of cancer increased at diagnosis and then declined over time.[139] The authors suggest that reverse causation and increased surveillance for cancer in the first few years following the diagnosis of diabetes may play a part in the increased incidence of cancer in people with type 2 diabetes observed.[139] However, in a meta-analysis conducted by Batabyal and colleagues, the risk of cancer was greatest soon after diagnosis of diabetes but diabetes remained a modest but true risk factor for pancreatic cancer.[140]

For other site specific cancers, the number of studies is small. However, in two observational studies, there was no evidence of an association between diabetes and ovarian[141] and lung cancer.[142] In two meta-analyses investigating a possible association between diabetes and thyroid cancer, one reported a significant increase and the other a non-significant increase in the incidence of thyroid cancer in people with diabetes.[143,144] In Japan, the incidence of gastric cancer is high and one prospective study carried out in the Japanese population found evidence of an association between a modest increase in fasting plasma glucose and gastric cancer, although the applicability of the results to other populations is not certain.[145]

Several meta-analyses have investigated the risk of mortality from cancer and determined that diabetes was associated with an increased risk of mortality from breast cancer,[59,122] lung cancer,[59,146] liver cancer and hepatocellular carcinoma,[59,135,136,147] ovary,[59] bladder[59] and colorectal cancer.[59,125,129,148] In a meta-analysis by the Emerging Risk Factors Collaboration, diabetes was associated with an increase in death from any cancer (RR 2.32, 95% CI 2.11–2.56).[59] Two further cohort studies based in the UK and the US found that the prognosis following incident cancer is poorer for people with diabetes.[149,150] A meta-analysis by Barone and colleagues found that people diagnosed with cancer and pre-existing diabetes have an increased risk of long-term all-cause mortality versus people without diabetes (HR 1.41, 95% CI 1.28-1.55).[151] In addition to the possible mechanisms linking cancer and diabetes, several other possible explanations for this association have been postulated including the effect of glucose-lowering therapy, differences in cancer treatments based on clinical decisions relating to diabetes-related conditions, poorer response to cancer treatment, presentation with later staged cancer due to differences in screening and

the effect of cancer treatment, for example glucocorticoids and anti-androgens, on diabetes control.[114,151]

2.1.4. All-cause mortality

The life expectancy of a person diagnosed with diabetes at the age of 40 is estimated to be around 6 years less than someone without diabetes.[59] A reduction in the risk of cardiovascular and all-cause mortality in people with diabetes[152–159] and type 2 diabetes specifically.[66] Conversely, one study has reported an increase in the mortality burden associated with type 2 diabetes between 1970 and 1994.[160] Life expectancy in type 2 diabetes has been shown to vary depending not only on glycaemic control but also on several risk factors, including blood pressure, the ratio of total:HDL cholesterol and diabetes duration.[161]

2.2. Influence of insulin therapy on adverse events

2.2.1. Mechanisms

2.2.1.1. Preservation of β cells

Insulin has been reported to be β cell protective through the facilitation of β-cell rest.[162] Short term infusion of insulin has been shown to augment glucose induced β-cell secretory response in healthy humans.[163] Eight weeks of treatment with insulin glargine in people with type 2 diabetes receiving metformin therapy has been demonstrated to increase first and second phase insulin secretion.[164] Early intensive insulin therapy in type 2 diabetes has been reported to be more likely to induce a sustained period of glycaemic remission in comparison with oral hypoglycaemic

agents.[165] The long term effects on β-cell function of intensified insulin therapy have been described in a recent review by Retnakaran and Zinman.[166]

A meta-analysis of seven studies (two of which were randomised) carried out in Asia found that short term intensive insulin therapy in people with early type 2 diabetes led to an improvement in beta cell function and insulin resistance.[167] Furthermore, when the results of the four studies (one randomised) examining glycaemic remission were combined, it was shown that a high proportion of people also achieved long term, drug free glycaemic remission (66.2% after 3 months, 58.9% after 6 months, 46.3% after 12 months and 42.1% after 24 months follow up).[167] However, a limitation of this meta-analysis is the lack of a comparator group, therefore potential beneficial effects of lifestyle interventions cannot be ruled out.[167]

2.2.1.2. Cardiovascular disease

The management of type 2 diabetes places emphasis on achieving normal glycaemic, lipid and blood pressure levels with the aim of reducing cardiovascular event risk. However, different classes of glucose-lowering therapies have their own mechanisms of action, which may lead to a different effect on cardiovascular risk. It has been postulated that insulin has an anti-inflammatory effect.[168,169] However, it has also been proposed that insulin may affect cardiovascular risk through several mechanisms. These mechanisms are described below.

2.2.1.2.1. Glucose-lowering effects

Insulin has a theoretically unlimited potential to lower blood glucose. In a pooled analysis of 11 RCTs, the addition of insulin glargine to existing glucose-lowering therapy in people with uncontrolled type 2 diabetes led to a reduction in HbA_{1c} to ≤7% at 24 weeks in 68.1%, 50.4% and 56.4% of patients treated with metformin monotherapy, sulfonylurea monotherapy and metformin plus sulfonylurea, respectively.[170] A decrease in HbA_{1c} following insulin initiation has also been reported in several other studies.[171–176] However, after an initial good response to insulin, glucose control has been shown to deteriorate more in obese people versus non-obese people.[177] A recent retrospective cohort study has shown that the mean HbA_{1c} for a population of type 2 diabetics using insulin was 8.3%.[178] The effect of intensive glucose lowering on cardiovascular outcomes is discussed in Chapter 2.2.2.1.

2.2.1.2.2. Hyperinsulinaemia

A meta-analysis showed that hyperinsulinaemia is a weak risk factor for the occurrence of cardiovascular disease.[179] Type 2 diabetes is characterised by relative insulin deficiency and insulin resistance. Hyperinsulinaemia is therefore a predictable consequence of the use of exogenous insulin in type 2 diabetes and has been linked to an increased risk of atherogenic effects.[180,181] Insulin resistance may also increase as a function of increasing levels of insulin, either through endogenous insulinaemia or through the use of exogenous insulin.[182] The administration of exogenous insulin may also lead to plasma concentrations of insulin that are supra-physiological. It has been hypothesised that, when exogenous insulin is injected into the adipose tissue, the concentration of insulin in the systemic circulation needs to be much higher than that

which occurs naturally in order for a sufficient concentration of insulin to reach the liver to control glucose production and/or uptake.[183] Conversely, Kruszynska and colleagues have reported that insulin can be administered to diabetic rats without causing hyperinsulinaemia.[184]

Ferrannini and colleagues have reported that insulin may be associated with possible negative (smooth muscle proliferation, vasoconstriction, extended QTc interval, fluid retention and prothrombotic) and positive (vasodilation, anti-inflammatory and antithrombotic) vascular effects.[185] A recent review has discussed how insulin may be pro-atherogenic, particularly in the presence of insulin resistance and pre-existing macrovascular disease where it has been hypothesised that impaired functioning of the phosphatidylinositol 3-kinase (PI3K) pathway and the overstimulation of the Mitogen-activated protein kinase (MAPK) pathway by insulin leads to the development of atherosclerotic plaques in vessel walls.[75] Insulin use has been hypothesised to increase angiogenesis within atherosclerotic plaques leading to plaque vulnerability, a predictor of future cardiovascular events.[186]

Insulin plays a role in several tissues. For example, in type 2 diabetes, the kidney and sympathetic nervous system remain sensitive to insulin, and hyperinsulinaemia can lead to sodium retention and increased sympathetic nervous system activity, which could increase blood pressure.[187] Two studies have shown that insulin may also reduce urinary sodium excretion in people with type 2 diabetes, however, the effect this has on blood pressure, is not clear.[188,189]

It has been hypothesised that insulin has antioxidant and anti-inflammatory effects which may protect against endothelial dysfunction and vascular disease[190] including

the suppression of ROS and adhesion molecule expression.[168] Insulin has also been reported to increase the production of nitric oxide leading to vascular dilatation.[168]

2.2.1.2.3. Hypoglycaemia

A limitation of intensive insulin therapy is the risk of hypoglycaemia, which occurs more frequently in people using insulin than other glucose-lowering therapies[191] and has been linked to dead-in-bed syndrome in type 1 diabetes.[192] A recent review article by Nordin has discussed the mechanism by which hypoglycaemia can lead to calcium overload and prolongation of the QT interval, an arrhythmogenic effect that is thought to be greatest in patients with pre-existing cardiovascular disease and diabetes.[76,193–196]

Zoungas and colleagues analysed data from the Action in Diabetes and Vascular Disease-Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study and found a strong association between severe hypoglycaemia and the risk of major macrovascular events, major microvascular events, cardiovascular death or death from any cause.[197] However, it is unknown whether severe hypoglycaemia contributes to these outcomes or whether people who experience hypoglycaemia are more likely to have other comorbidities which may increase their risk of these outcomes.[197]

Stahn and colleagues have recently found that people with type 2 diabetes and a prior history of cardiovascular disease treated with insulin and/or sulfonylureas experienced a high incidence of asymptomatic severe episodes of hypoglycaemia and silent severe arrhythmias.[198] A recent study documented that patients who received insulin doses of ≥0.6 units/kg were at increased odds of hypoglycaemia.[199] After multifactorial

adjustment, the higher odds of hypoglycaemia with increasing insulin doses remained (0.6–0.8 units/kg: odds ratio (OR) 2.10, 95% CI 1.08–4.09; 0.8 units/kg: 2.95, 1.54–5.65). In contrast, the adjusted odds of hypoglycaemia were no higher in patients who received only 0.2–0.6 units/kg.

In the ORIGIN study, severe hypoglycaemia occurred significantly more often in patients randomised to insulin glargine compared with those in the control arm, despite the low insulin requirement (6.3% vs. 1.8%; p<0.001).[80] In a report from the ORIGIN trial, severe hypoglycaemia was associated with a greater risk of mortality (adjusted hazard ratio (aHR) 1.74, 95% CI 1.39–2.19), cardiovascular death (1.71, 1.27–2.30), and arrhythmia-related death (1.77, 1.17–2.67). However, the severe hypoglycaemia hazard for all outcomes was higher with standard care than with regimens that included low-dose insulin glargine.[200]

Results from two meta-analyses suggest that hypoglycaemia counteracts any benefits associated with intensive glucose-lowering treatment.[201,202] In a study conducted by McCoy and colleagues, patients who report severe hypoglycaemia were at a 3.4 (95% CI 1.5–7.4) fold increased risk of death when compared with those who report mild or no hypoglycaemia.[203]

2.2.1.2.4. Weight gain

Weight gain is a common side effect of insulin therapy[80,204,205] which could be due in part to the anabolic effect of insulin and increased calorie intake due to patients' fear of hypoglycaemia.[206,207] In a three-year, open-label, multicentre trial, the use of biphasic, prandial and basal insulin were associated with an increase in weight from baseline of 5.7kg, 6.4kg and 3.6kg, respectively.[208] Insulin use has been associated with

an increase in weight in several RCTs.[80,171,209,210] In a study using mice, Mehran et al have suggested that hyperinsulinaemia may play a causal role in the development of obesity.[211]

Weight is associated with increased cardiovascular risk and cancer rates in non-diabetics.[118] Weight gain increases the risk of coronary heart disease and as such should be minimised in type 2 diabetes. [212,213]

2.2.1.3. Cancer

Diabetes medications can influence the risk of cancer through their effects on risk factors that are common to both diabetes and cancer, for example weight and hyperglycaemia.[115] However, different classes of glucose-lowering medicines have different mechanisms of action and are therefore also associated with different cancer risks.

Insulin is a growth factor and may therefore affect cancer progression through the interaction with insulin receptors which have been shown to be overexpressed on various types of cancer cells.[77,214] The risk of cancer may also vary depending on the type of insulin administered. For example several studies have shown that insulin glargine may have a higher mitogenic potency compared with other insulin analogues and human insulin due to its increased binding affinity to the IGF-1 receptor.[215] The use of insulin in the presence of insulin resistance can cause hyperinsulinaemia. In addition, insulin can cause weight gain.[80,204,205] As described in Chapter 2.1.3, both hyperinsulinaemia and obesity have been associated with an increased risk of cancer.

2.2.2. Description of studies comparing the risk of cardiovascular disease and cancer risk in people treated with and without insulin

2.2.2.1. Intensive glycaemic control in type 2 diabetes

Insulin has a theoretically unlimited potential to lower blood glucose. Poorly controlled, inadequately treated diabetes is associated with an increased risk of microvascular complications in type 1[216] and type 2 diabetes.[67,82] In recent years, several landmark RCTs have investigated the effect of intensive glycaemic control on macrovascular and microvascular outcomes.

The UKPDS recruited 3,867 people with newly diagnosed type 2 diabetes and randomised them to receive intensive glucose-lowering treatment with insulin or sulfonylureas or conventional treatment with diet only.[67] Patients were followed up for ten years.[67] The target fasting plasma glucose (FPG) in the intensive group was <6mmol/l.[67] In the conventional group, the target HbA_{1c} was the best achievable with diet alone and other glucose-lowering therapies were only initiated if FPG levels exceeded 15mmol/l or the patient developed symptoms of hyperglycaemia.[67] Versus conventional treatment, intensive control of blood glucose reduced microvascular risk by 25% (95% CI 7–40%, p=0.0099) but the effect on macrovascular outcomes was not statistically significant (HR myocardial infarction 0.84, 95% CI 0.71–1.00; and stroke HR 1.11, 95% CI 0.81–1.51).[67] It was not until the follow-up observational study was carried out ten years later that the cardiovascular benefits associated with intensive glucose control became apparent.[112] Even though the difference in HbA_{1c} between treatment arms was lost after one year, the risk of microvascular disease (risk reduction of 24%, p=0.001), myocardial infarction (risk reduction of 15%, p=0.01) and all-cause mortality (risk reduction of 13%, p=0.007) was lower for patients originally

randomised to receive intensive treatment after the 10-year follow-up.[112] The authors postulated that this was a legacy effect of their prior randomization to receive intensive glucose control during the trial period.[112]

Following on from this, three more large RCTs provided relevant data: the ACCORD study, ADVANCE and the Veterans Affairs Diabetes Trial (VADT). Unlike UKPDS—which only included people newly diagnosed with type 2 diabetes—these three trials included a larger proportion of patients with pre-existing cardiovascular disease. During the ACCORD study, the intensive-treatment arm was associated with a non-significant 10% reduction in the composite primary outcome, but it was terminated early after three and a half years due to an unexplained excess of all-cause mortality in this group.[79] When the outcomes for patients with the same HbA_{1c} levels (above 7%) were compared within groups, it found that people in the intensive treatment arm were worse off. A recent review article hypothesised that high doses of insulin may have been used in order to achieve low HbA_{1c} values and that this may have contributed to the increased cardiovascular risk in intensively treated ACCORD patients.[75] The VADT and the ADVANCE trials also did not demonstrate that intensive treatment was associated with a reduced risk of macrovascular events.[217,218] Subgroup analysis of ACCORD found that people with no prior cardiovascular events or a HbA_{1c} of ≤8% in the intensively treated arm had fewer fatal or non-fatal cardiovascular events when compared to standard treatment (p for interaction = 0.04 and 0.03, respectively).[79] Conversely, in the ADVANCE trial, the results were similar across all subgroups.[218]

Several meta-analyses of available long-term trials, including UKPDS, ACCORD, ADVANCE and VADT, have been carried out. In the largest and most recently published

meta-analysis by Hemmingsen and colleagues, intensive versus conventional management of blood glucose was not associated with a significantly different risk in all-cause or cardiovascular mortality but a reduction in the risk of non-fatal myocardial infarction was reported (RR 0.87, 95% CI 0.77–0.98).[111] The risk of a composite outcome of microvascular disease was significantly reduced with intensive glycaemic control (RR 0.88, 0.82–0.95).[111] However a high risk of bias was detected in many of the included trials.[111] The meta-analysis of 13 RCTs carried out by Boussageon and colleagues did not find evidence of a significant decrease in the risk of all-cause mortality (RR 1.04, 99%CI 0.91–1.19) or cardiovascular death (1.11, 0.86–1.43) with intensive therapy but a reduction in the risk of non-fatal myocardial infarction (0.85, 0.740.96) was observed.[202] The meta-analysis by Mannucci and colleagues adopted stricter inclusion criteria and included only those RCTs where the between-group difference in mean HbA_{1c} during the trial was at least 0.5% and the planned duration of treatment was at least 3 years.[201] A significant reduction in the risk of cardiovascular events and myocardial infarction was observed in the intensively treated group when compared with conventional therapy.[201] However, the reductions in stroke and cardiovascular mortality were not significant.[201] The meta-analysis by Turnbull and colleagues including only UKPDS, VADT, ACCORD and ADVANCE found a 15% reduction in fatal and non-fatal myocardial infarction in the more intensively treated group (HR 0.85, 95% CI 0.76– 0.94) but no significant reduction in all-cause mortality (HR 1.04,95% CI 0.90–1.20) or cardiovascular death (1.10 95% CI 0.84–1.42).[219] Post hoc analyses of ACCORD and ADVANCE found that severe hypoglycaemia was associated with an increased risk of mortality but this finding may not account for the differences in mortality between study arms.[197,220]

In the Steno-2 study, 80 patients were randomised to receive conventional therapy and 80 patients were assigned to receive intensive management targeting multiple risk factors including hyperglycaemia, hypertension, dyslipidaemia and microalbuminuria using a combination of behaviour modification and pharmacologic therapy.[221] Intensive intervention reduced the risk of cardiovascular and microvascular events by approximately 50% in people with type 2 diabetes and microalbuminuria.[221]

An epidemiological study using data from CPRD published in *The Lancet* reported that, in people with type 2 diabetes, low HbA_{1c} levels were associated with an increased risk of all-cause mortality and cardiac events as well as high levels in a U-shaped association.[60] A similar type of association has also been observed in other epidemiological studies. Nicholas and colleagues conducted a case-control study, again using data from CPRD, and found that HbA_{1c} levels <6.5% and >9.0% may be associated with an increased risk of mortality within one year for people with type 2 diabetes.[222] A further nested case-control study using data from the Kaiser Permanente Southern California Health Plan demonstrated that patients with type 2 diabetes and a HbA_{1c} level of ≤6% and >8% over a three year period were at increased risk of cardiovascular events compared with people with a mean HbA_{1c} level of >6% and ≤8%.[223] Ostgren and colleagues found that the J-shaped association between HbA_{1c} and cardiovascular or all-cause mortality in type 2 diabetes was most pronounced in patients with a low educational level (HR for the lowest HbA_{1c} decile was 1.6, 95% CI 1.2–2.1, for the low educational group and 1.2, 0.8–1.6, for the high educational category).[224]

Although current guidelines recommend a target HbA_{1c} of less than 7% (53 mmol/mol) for many people with diabetes, they also suggest that treatment targets should be individualised, taking into consideration a patient's additional coexisting medical

conditions, life expectancy, history of hypoglycaemia and presence of diabetes complications.[7]

2.2.2.2. A systematic review of meta-analyses characterising the safety of exogenous insulin in type 2 diabetes

2.2.2.2.1. Introduction

Various observational studies have shown an association between the use of exogenous insulin in type 2 diabetes and the risk of cancer, cardiovascular events and all-cause mortality.[60–62,223] However, observational studies can be associated with a risk of confounding.

In terms of the Oxford Centre for Evidence Based-Medicine 2011 levels of evidence, systematic reviews rank highly, occupying Step 1 when investigating the benefits and harms of treatment.[225] The use of well-conducted meta-analysis to combine available data to produce an integrated result can be a powerful tool to summarise existing evidence. Therefore, the aim of this review was to identify relevant meta-analyses to characterise the pool of existing evidence relating to the safety of injecting insulin in people with type 2 diabetes, specifically the association between insulin use and the risk of all-cause mortality, cardiovascular events and cancer in type 2 diabetes compared with other glucose-lowering medicines.

2.2.2.2.2. Methods

We carried out a systematic search of the Web of Knowledge database to March 2014 to identify relevant meta-analyses published in the previous five years. Obviously, these meta-analyses themselves reviewed constituent studies from a much longer observational period (1975–2013). The matches were restricted by publication type and only articles and reviews were retrieved. The search terms used are listed in the Table 2.1. Articles were included if: (1) they compared the effect of insulin versus at

least one other class of glucose-lowering agent; (2) the study population was composed solely of people with type 2 diabetes; (3) the investigated endpoints included at least one of all-cause mortality, cancer, cancer related mortality, cardiovascular events or cardiovascular death; (4) the article was available in the English language. Meta-analyses investigating only hospitalised or seriously ill people with type 2 diabetes were excluded. The citations of all studies included in the selected meta-analyses were also reviewed to identify any further, relevant meta-analyses detailed in the manuscript. Identified studies were screened using title, abstract and full text where necessary and those studies that did not answer the pre-specified research question were excluded at this stage.

2.2.2.2.3. Results

Of a total of 906 articles identified using the search strategy, seven meta-analyses were relevant and included in this review (Figure 2.1 and Table 2.2). The findings in terms of the risk of progression to respective events from these meta-analyses are summarised in Figure 2.2.

Table 2.1 Search terms used in the Web of Knowledge Database

Search Number	Logic	Search term	
Mortality	1st	Diabetes* AND "meta-analysis" AND insulin AND * mortality OR diabetes* AND "systematic review" AND insulin AND *mortality OR diabetes* AND "meta analysis" AND insulin AND *mortality	Title
	OR	Diabetes* AND "meta-analysis" AND insulin AND * mortality OR diabetes* AND "systematic review" AND insulin AND *mortality OR diabetes* AND "meta analysis" AND insulin AND *mortality	Topic
	NOT	"type 1" or gene*	Topic
Death	1st	Diabetes* AND "meta-analysis" AND insulin AND death OR diabetes* AND "systematic review" AND insulin AND death OR diabetes* AND "meta analysis" AND insulin AND death	Title
	OR	Diabetes* AND "meta-analysis" AND insulin AND death OR diabetes* AND "systematic review" AND insulin AND death OR diabetes* AND "meta analysis" AND insulin AND death	Topic
	Not	"type 1" or gene* or *mortality	Topic
Cancer	1st	Diabetes* AND "meta-analysis" AND insulin AND cancer OR diabetes* AND "systematic review" AND insulin AND cancer OR diabetes* AND "meta analysis" AND insulin AND cancer	Title
	OR	Diabetes* AND "meta-analysis" AND insulin AND cancer OR diabetes* AND "systematic review" AND insulin AND cancer OR diabetes* AND "meta analysis" AND insulin AND cancer	Topic
	Not	"type 1" or gene* or *mortality or death	Topic
Cardio-vascular (a)	1st	Diabetes* AND "meta-analysis" AND insulin AND cardi* OR diabetes* AND "systematic review" AND insulin AND cardi* OR diabetes* AND "meta analysis" AND insulin AND cardi*	Title
	OR	Diabetes* AND "meta-analysis" AND insulin AND cardi* OR diabetes* AND "systematic review" AND insulin AND cardi* OR diabetes* AND "meta analysis" AND insulin AND cardi*	Topic
	Not	"type 1" or gene* or *mortality or death or cancer	Topic

Cardio-vascular (b)	1st	Diabetes* AND “meta-analysis” AND insulin AND heart* OR diabetes* AND “systematic review” AND insulin AND heart* OR diabetes* AND “meta analysis” AND insulin AND heart*	Title
	OR	Diabetes* AND “meta-analysis” AND insulin AND heart* OR diabetes* AND “systematic review” AND insulin AND heart* OR diabetes* AND “meta analysis” AND insulin AND heart*	Topic
	Not	“type 1” or gene* or *mortality or death or cancer or cardi*	Topic
Cardio-vascular (c)	1st	Diabetes* AND “meta-analysis” AND insulin AND myocard* OR diabetes* AND “systematic review” AND insulin AND myocard* OR diabetes* AND “meta analysis” AND insulin AND myocard*	Title
	OR	Diabetes* AND “meta-analysis” AND insulin AND myocard* OR diabetes* AND “systematic review” AND insulin AND myocard* OR diabetes* AND “meta analysis” AND insulin AND myocard*	Topic
	Not	“type 1” or gene* or *mortality or death or cancer or cardi* or heart*	Topic
Cardio-vascular (d)	1st	Diabetes* AND “meta-analysis” AND insulin AND stroke OR diabetes* AND “systematic review” AND insulin AND stroke OR diabetes* AND “meta analysis” AND insulin AND stroke	Title
	OR	Diabetes* AND “meta-analysis” AND insulin AND stroke OR diabetes* AND “systematic review” AND insulin AND stroke OR diabetes* AND “meta analysis” AND insulin AND stroke	Topic
	Not	“type 1” or gene* or *mortality or death or cancer or cardi* or myocard*	Topic

Table 2.2 Summary of identified meta-analyses

First author, year	N of studies included (events)	Selection criteria	Intervention	Duration of included studies	Sources of search	Quality of included studies
Monami and colleagues, 2013[226]	5 (665) for all-cause mortality 5 (354) for CV death 2 (487) for CV events	(1) RCTs (2) study duration of ≥24 weeks (3) patients with type 2 diabetes (4) sulfonylureas compared with placebo or other classes of glucose-lowering medicines	SUs vs placebo or other classes of glucose-lowering medicines	24-577 weeks	Medline, Embase, Cochrane. Results of unpublished trials retrieved from www.clinicaltrials.gov, www.merck.com/mrl/clinical_trials/results.html, www.novartisclinicaltrials.com, www.clinicalstudyresults.org and the Food and Drugs Administration (FDA) and European Medicines Agency (EMA) websites.	Assessed using some of the parameters proposed by Jadad and colleagues[227] The quality of the retrieved trials was heterogeneous.
Wang and colleagues, 2013[228]	4 (3326)	(1) Original articles of a quantitative assessment of the relationship of insulin therapy and the risk of colorectal cancer (2) Cohort studies (3) Adult, human population (4) Main independent variable is insulin (5) Results are expressed as RRs and 95% CI is provided or can be calculated (6) Estimates have been adjusted for age and gender.	Insulin vs no insulin	Not recorded	Medline, PubMed, Web of Science, Embase, Chinese Biomedical Literature Database (CBM). No date restriction was applied	Not assessed

Colmers and colleagues, 2012[229]	Ever insulin Vs other glucose-lowering medicines: 10 (≥3838) for colorectal cancer 4 (≥3201) for breast cancer 3 (≥3325) for prostate cancer. New insulin versus other types of glucose-lowering medication: 3 (≥2688) for breast cancer 2 (≥2582) for prostate cancer 3 (≥1300) for pancreatic cancer	(1) Cohort or nest case-control studies (2) Patients with type 2 diabetes (3) Outcome of incident cancer at any site or incident cancer overall (4) Insulin versus other glucose-lowering medicines or insulin glargine Vs other insulin types (5) Written in English	Insulin vs other glucose-lowering medicines	≤5.8 years but not recorded for all included studies	Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Review Effects, Health Technology Assessment, Cochrane Central Register of Controlled Trials, Science Citation Index Expanded, Conference Proceedings Citation Index - Science, Scopus, reference list of included studies and consultation with experts in the field. Date range not specified.	Assessed using the Newcastle-Ottawa scale. Mean=6.9 out of 8 and no studies were assessed to be at a high risk of bias
Singh and colleagues, 2013[230]	7 (22,611)	(1) RCTs or observational studies (2) Evaluated and clearly defined exposure to anti-diabetic medication (3) Reported HCC incidence in patients with diabetes (4) reported RR or OR or enough data provided for their calculation	Insulin vs no insulin	≤5 years but not recorded for all included studies	Medline, Embase and Web of Science from 1966 to 1st Aug 2012 and also abstracts from major gastroenterology conferences	Assessed using the Newcastle-Ottawa scale. Included studies ranged from 6 to 9 (where 9 was the maximum possible score).

Hemmingsen and colleagues, 2013[231]	FGS vs insulin: 2 (370) for all-cause mortality 2 (214) for CV mortality 2 (168) for non-fatal MI 2 (92) for cancer. SGS vs insulin: 4 (309) for all-cause mortality 4 (175) for CV mortality 2 (76) for cancer.	(1) RCTs (2) participants ≥18 years old (3) participants with type 2 diabetes (4) participants treated with SU monotherapy (5) study duration of ≥ 24 weeks	FGS or SGS vs insulin	FGS vs insulin: 4.75 to 10 years for all-cause mortality, CV death, non-fatal MI or cancer. SGS vs insulin: 9mths to 10 years for all-cause mortality and CV mortality, 6 to 10 years for cancer	The Cochrane Library, MEDLINE, EMBASE, Science Citation Index Expanded, LILACS, CINAHL (all until Aug 2011)	GRADE Working Group grades of evidence used to assess quality. All relevant pooled analyses were scored as low quality indicating that further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate
Janghorbani and colleagues, 2012[232]	8 (number of incident cancers = 3,169, number of cancer-related deaths = 249)	(1) Original articles (2) Case-control or cohort studies (3) Adult human population (4) Insulin use as the main independent variable.	Insulin vs no insulin	Not stated	PubMed, ISI, EMBASE through January 2011	Not assessed.

Franciosi and colleagues, 2013[233]	Observational and RCTs included for metformin vs no metformin. However, the type of studies included in the meta-analysis for metformin vs insulin is unknown	(1) RCT enrolling people with diabetes treated with metformin compared with a control group (2) Cohort, case control or nested case-control studies of patients with diabetes reporting on metformin exposure and cancer incidence/ prevalence or mortality (3) Studies in which exposure to metformin was assessed from prescription databases and incidence of cancer was derived from cancer registries (4) Treatment exposure of ≥24 weeks (5) Studies in humans (6) Studies published in English language only. Studies where metformin was used to treat other conditions (e.g. PCOS, metabolic syndrome) were excluded.	Metformin vs insulin	≥24 weeks. Maximum length unknown as studies included in metformin insulin comparison not defined.	Medline and Embase from 1966 to April 2012.	Methodological quality of RCTs assessed using risk bias tool exploring the following domains: (1) Random sequence generation (2) Allocation concealment (3) Blinding of investigators, participants and outcome assessments (4) Use of intention to treat analysis (5) Completeness of follow-up. For observational studies, the following was assessed: (1) Selection of participants (2) Measurement of prognostic factors and outcomes (3) Adjustment for confounding (4) Quality of the analysis. Risk of bias presented for the 53 studies (12 RCTs, 41 observational) included in the meta-analysis but it is unclear how this referred to the studies included in the metformin vs insulin comparison

CV = cardiovascular, SU = sulfonylurea, SGS = second generation sulfonylurea, FGS = first generation sulfonylurea, MI = myocardial infarction, PCOS = polycystic ovary syndrome

Figure 2.1 Flow diagram summarising study identification and selection

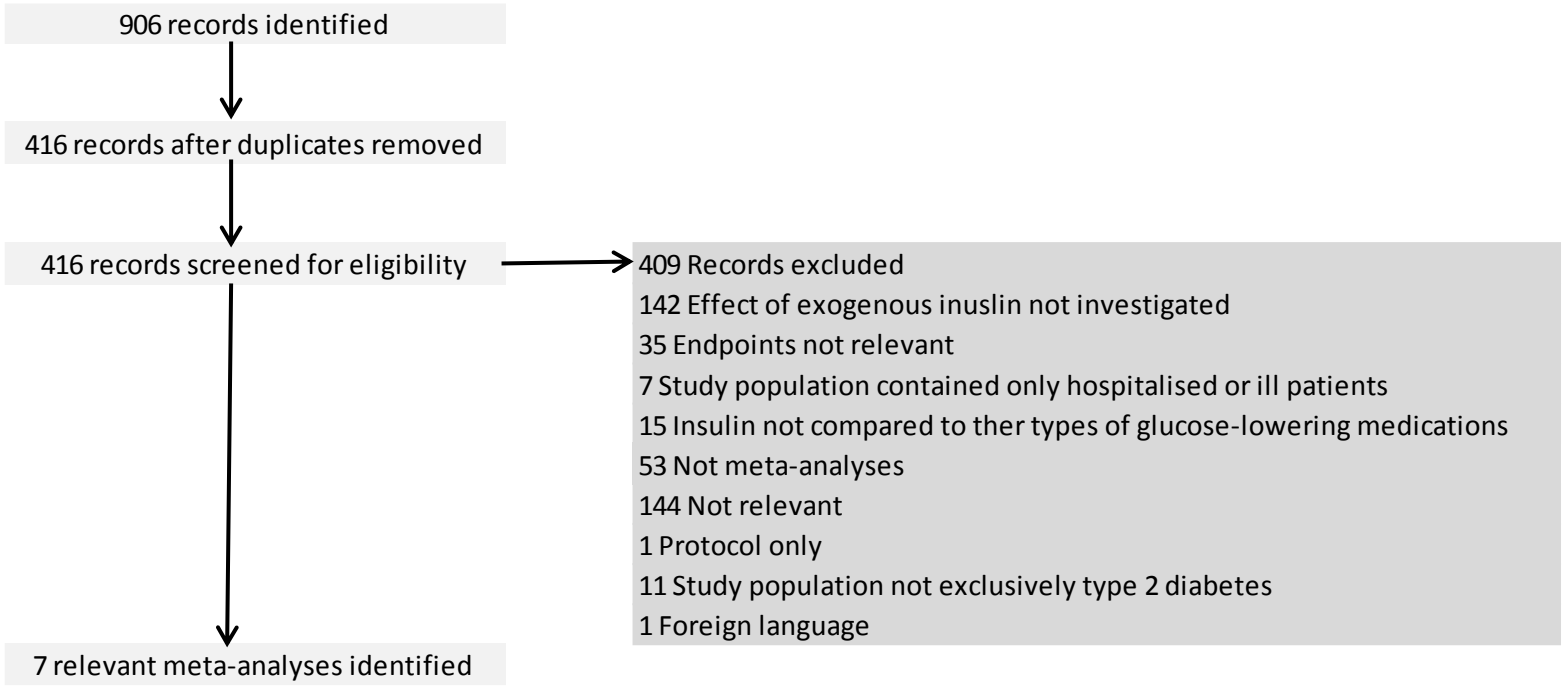
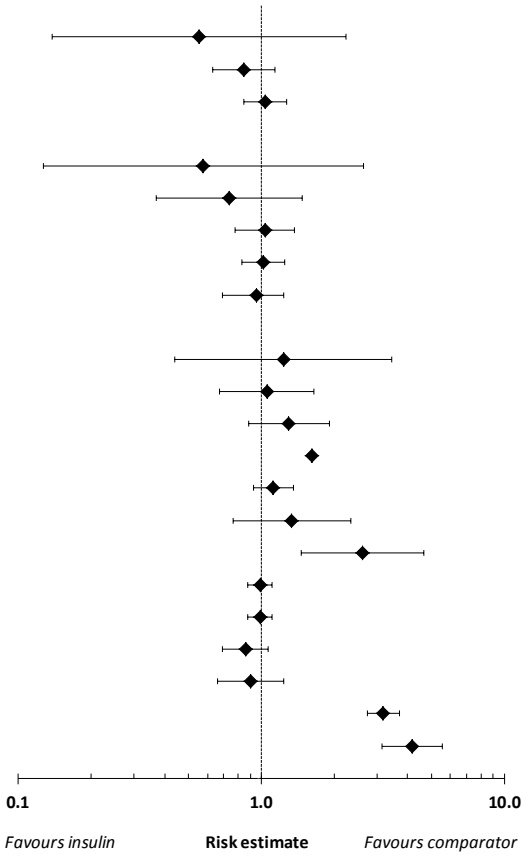


Figure 2.2 Summary of the results from the identified and relevant meta-analyses



Endpoint	Author	Risk estimate	Comparator
All-cause mortality	Monami (2013)	MH-OR 0.56 (0.14-2.22)	Insulin Vs SU
	Hemmingsen (2013)	RR 0.85 (0.63-1.14)	Insulin Vs FGS
	Hemmingsen (2013)	RR 1.04 (0.85-1.27)	Insulin Vs SGS
Cardiovascular			
CV death	Monami (2013)	MH-OR 0.58 (0.13-2.63)	Insulin Vs SU
CV death	Hemmingsen (2013)	RR 0.74 (0.37-1.47)	Insulin Vs FGS
CV death	Hemmingsen (2013)	RR 1.04 (0.78-1.37)	Insulin Vs SGS
CV event	Monami (2013)	MH-OR 1.02 (0.83-1.25)	Insulin Vs SU
Non-fatal MI	Hemmingsen (2013)	RR 0.95 (0.69-1.23)	Insulin Vs FGS
Cancer			
Any cancer	Hemmingsen (2013)	RR 1.23 (0.44-3.45)	Insulin Vs FGS
Any cancer	Hemmingsen (2013)	RR 1.05 (0.67-1.64)	Insulin Vs SGS
Incident cancer or cancer-related death	Janghorbani (2012)	RR 1.30 (0.89-1.90)	Insulin Vs No insulin
Colorectal cancer	Wang (2013)	RR 1.61 (1.18-1.35)	Ever ins Vs other glucose-lowering med
Colorectal cancer	Colmers (2012)	RR 1.12 (0.93-1.35)	Ever insulin versus other glucose-lowering meds
Colorectal cancer	Franciosi (2013)	OR 1.33 (0.76-2.33)	Insulin Vs Metformin
Hepatocellular cancer	Singh (2013)	OR 2.61 (1.46-4.65)	Insulin Vs No insulin
Breast cancer	Colmers (2012)	RR 0.99 (0.88-1.11)	Ever insulin versus other glucose-lowering meds
Breast cancer	Colmers (2012)	RR 0.99 (0.88-1.11)	New insulin versus other glucose-lowering meds
Prostate cancer	Colmers (2012)	RR 0.86 (0.69-1.07)	Ever insulin versus other glucose-lowering meds
Prostate cancer	Colmers (2012)	RR 0.90 (0.66-1.24)	New insulin versus other glucose-lowering meds
Pancreatic cancer	Colmers (2012)	RR 3.18 (2.73-3.71)	New insulin versus other glucose-lowering meds
Pancreatic cancer	Franciosi (2013)	OR 4.17 (3.13-5.56)	Insulin Vs Metformin

When necessary, the reciprocal of the risk estimate was taken to ensure that insulin exposure was always the reference category.

2.2.2.2.3.1. Cardiovascular events and all-cause mortality

Two meta-analyses were identified that investigated the association between insulin and all-cause mortality or cardiovascular events. Monami and colleagues combined five RCTs and found that people with type 2 diabetes using sulfonylureas had an increased risk of all-cause mortality (Mantel-Haenszel odds ratio (MH-OR) 1.80, 95% CI 0.45–7.26) and cardiovascular death (MH-OR 1.73, 95% CI 0.38–7.88) compared with insulin but these results were not statistically significant.[226] Two RCTs were combined to determine that the risk of major cardiovascular events was also not significantly greater for people using sulfonylureas versus insulin (MH-OR 0.98, 95% CI 0.80–1.20).[226] A Cochrane systematic review of RCTs found that there was no significant difference in the risk of all-cause mortality (RR 1.18, 95% CI 0.88–1.59) and cardiovascular death (RR 1.36, 0.68–2.71) associated with FGSs compared with insulin.[231] A non-significant result was also found for SGSs compared with insulin (RR 0.96, 0.79–1.18, for all-cause mortality and 0.96, 0.73–1.28, for cardiovascular death).[231]

2.2.2.2.3.2. Cancer

Six meta-analyses investigated the association between insulin use and the risk of cancer in type 2 diabetes.[228–233] Singh and colleagues combined seven observational studies—two cohort studies and five case-control studies) and found that the risk of hepatocellular cancer was significantly higher for people with type 2 diabetes using insulin compared with no insulin use (adjusted OR = 2.61, 95% CI 1.46–4.65).[230] Wang and colleagues analysed four studies (one case-control and three cohort studies) and found that, compared with no insulin use, insulin use in type 2 diabetes was associated

with an increased risk of colorectal cancer (RR=1.61).[228] However, there appeared to be an error in the 95% confidence intervals, which were detailed as 1.18–1.35.[228] In a meta-analysis of cohort and case-control studies, Colmers and colleagues found that there was an increased risk of pancreatic cancer associated with new users of insulin compared with no use of insulin in people with type 2 diabetes (RR 3.18, 95% CI 2.73–3.71) but the association between insulin use and the risk of colorectal, breast or prostate cancer was non-significant.[229] The Cochrane systematic review of RCTs conducted by Hemmingsen and colleagues did not identify any significant increase in the risk of cancer for first or SGSs versus insulin therapy in type 2 diabetes (RR 0.81, 95% CI 0.29–2.27, and 0.95, 0.61–1.49, respectively).[231] Janghorbani and colleagues combined the results of one case control study and seven cohort studies and found that the use of insulin in type 2 diabetes was associated with a non-significant increase in the risk of incident cancer and cancer related death (RR 1.30, 95% CI 0.89–1.90).[232] The meta-analysis by Franciosi and colleagues,[233] found that the use of metformin was associated with a non-significant reduction in the risk of colorectal cancer (OR 0.75, 95% CI 0.43–1.31) and a significant reduction in the risk of pancreatic cancer (OR 0.24, 0.18–0.32) when compared with insulin.

2.2.2.2.4. Discussion

Two meta-analyses investigating the effect of insulin on the risk of all-cause mortality and cardiovascular events and six meta-analyses investigating the association between insulin use and cancer were identified. Insulin use was found to be significantly associated with an increased risk of hepatocellular cancer (OR 2.61, 95% CI 1.46–4.65)[230] and pancreatic cancer (3.18, 2.73–3.71).[229] Insulin was also associated with a

significantly increased risk of pancreatic cancer when compared with metformin (OR for metformin vs. insulin = 0.24, 95% CI 0.18–0.32).[233] Most of the other associations were not significant.

The ORIGIN trial is one of the few RCTs to investigate the effect of insulin on the risk of cancer and cardiovascular outcomes. As the results were only published in June 2012, it was not included in any of the meta-analyses identified for this review. This was a large scale, long-term study in which 12,612 people with type 2 diabetes and pre-existing cardiovascular disease were followed up for a median of 6.2 years.[80] ORIGIN found that compared with standard treatment, the use of insulin glargine over a six year period had a non-significant effect on cardiovascular outcomes (HR 1.02, 95% CI 0.94–1.11 for cardiovascular death, non-fatal myocardial infarction or nonfatal stroke) and cancer (HR 1.00, 0.88–1.13).[80] In terms of site-specific cancers, insulin glargine was also found to have a non-significant effect on the risk of breast, colon and prostate cancers. The meta-analyses by Hemmingsen and colleagues also found that there was no significant increased risk of cancer associated with insulin compared with sulfonylureas.[231] Colmers and colleagues found that the risk of new or ever-use of insulin was not associated with an increased risk of breast, prostate or colorectal cancer versus no insulin use.[229] The lack of an association between insulin and the risk of prostate cancer is not that surprising considering that diabetes is associated with a reduced risk of prostate cancer, possibly due to lower circulating levels of testosterone.[234,235] The increased risk of cancer and cancer related death associated with insulin use was also not significant in the meta-analysis conducted by Janghorbani and colleagues[232] but a significant increased risk of hepatocellular cancer was found by Singh and colleagues.[230] However, the ORIGIN trial did not investigate pancreatic and hepatocellular cancers specifically. The results from the meta-analyses from

Monami and colleagues and Hemmingsen and colleagues determined that compared with sulfonylureas, the risk of death from all causes, cardiovascular death and cardiovascular events was not significantly different for insulin, a finding similar to the one reported from the ORIGIN trial. However, it is important to note that the comparison groups were not identical (sulfonylureas versus standard care).

Sulfonylureas stimulate insulin secretion and can cause weight gain and hypoglycaemia and may therefore adversely affect cardiovascular risk.[212,213] Some sulfonylureas may also impair a cardioprotective mechanism known as ischaemic preconditioning.[236] In addition, epidemiological data have shown that, compared with metformin, all-cause mortality and MACE was raised for both sulfonylureas (1.75, 95% CI 1.64–1.86 and 1.39, 1.25–1.55, respectively) and insulin monotherapy (2.20, 1.98–2.43 and 1.74, 1.44–2.09, respectively).[61] Therefore, the nature of the comparator is important in terms of the interpretation of the results and further studies comparing insulin use with other glucose-lowering agents are required.

Patients included in the ORIGIN study were in general newly diagnosed with type 2 or IGT, IFG or only using one glucose-lowering therapy. The baseline HbA_{1c} was also only 6.4%. This HbA_{1c} is low in comparison with ACCORD, ADVANCE and VADT at 8.1%, 7.5% and 9.4%, respectively.[79,217,218] Furthermore, the reduction in HbA_{1c} achieved during the trial was just 0.2% (in comparison with reductions of 1.4% for ACCORD, 1% for ADVANCE and 2.5% for VADT).[79,217,218] In addition, the insulin dose was relatively low after six years (0.40 units per kilogram; interquartile range, 0.27 to 0.56). It has been suggested that the selection of this study population helped to minimise the argument that any association between insulin use and cardiovascular risk could be attributed to its use in people with more advanced type 2 diabetes.[237] However, it also meant that

the people receiving insulin were not necessarily typical of people who would normally receive insulin in the real world. There was considerable cross contamination of other glucose-lowering therapies between groups (e.g. 65% of the insulin glargine group were also using other glucose-lowering agents, including 46.5% of patients using metformin, and 11% of the standard care group were using insulin).[80] Metformin may therefore have mitigated any risk associated with insulin but to an unidentifiable extent.

There were some limitations associated with the identified meta-analysis. Only two meta-analyses examining the use of insulin and the risk of cardiovascular events or all-cause mortality in type 2 diabetes were identified. The meta-analysis conducted by Monami and colleagues found that there were limitations in trial quality and many of the studies identified did not provide information on cardiovascular events and mortality. At least four of the meta-analyses investigating the use of insulin and the risk of cancer included only observational studies. The heterogeneity in the RR for the association between insulin treatment and cancer incidence and mortality in the meta-analysis conducted by Janghorbani and colleagues was high (I^2=89.0%, $P_{Heterogeneity}$=<0.01).[232] In addition, the meta-analysis combined the results from studies reporting cancer related deaths with studies reporting incident cancers and the quality of the included studies was not assessed.[232] In the meta-analysis conducted by Singh and colleagues, considerable heterogeneity was identified among the included studies (Cochran's Q test p<0.001, and I^2 = 88).[230] In addition, the included studies failed to adjust for possible confounders, most notably exposure to statins, which have been shown to reduce the risk of hepatocellular cancer.[230] A high risk of bias was attached to the RCTs used to generate the pooled estimates from the Cochrane systematic review.[231] The quality of the studies included in the meta-analysis conducted by Wang

and colleagues were not assessed and although heterogeneity was assessed using the Q statistic and the I^2 statistic, these results were not presented in the paper.[228] In addition, the number of studies excluded and the reason for exclusion was not provided. Colmers and colleagues suggested that the results of their meta-analysis should be interpreted with caution due to potential sources of heterogeneity within studies.[229] In fact, statistical heterogeneity was too large to be able to obtain a pooled estimate for the overall risk of pancreatic and any cancer associated with the ever-use of insulin and the risk of colorectal or any cancer with the new use of insulin. Heterogeneity was also high in the meta-analysis by Franciosi and colleagues investigating the risk of colorectal cancer associated with metformin use compared with insulin. Several of the meta-analyses investigated the association between insulin use and cancer risk compared with no insulin use.[229,230,232] Patients often take a combination of glucose-lowering therapies concomitantly and different glucose-lowering medications may have different inherent cancer-modifying effect, e.g. metformin may reduce the risk of cancer through the activation of the 5' adenosine monophosphate-activated protein (AMP) kinase pathway.[238] If the distribution of these concomitant medications is not the same across the two groups, this may result in an over- or under-estimation of the cancer risk associated with insulin.

Meta-analyses of observational studies are still exposed to the same criticism of confounding by indication as individual observational studies and differences in the design of combined studies may also lead to bias.[239] However, Ioannidis and colleagues have suggested that both RCTs and observational studies have their own individual merits.[240] Furthermore, studies have shown that observational studies do not necessarily overestimate effect compared to RCTs.[240] There is a lack of RCTs investigating the effect of insulin compared with glucose-lowering medicines other

than sulfonylureas on hard clinical endpoints such as MACE, cancer or all-cause mortality, and only two meta-analyses of RCT data were identified as part of our search strategy. With the exception of ORIGIN, whose results have only been recently published in 2012, the major landmark diabetes trials conducted in the last couple of decades, UKPDS, VADT, ACCORD and ADVANCE, investigated the effect of intensive control of blood glucose on the risk of microvascular and macrovascular complications.[67,79,217,218] As these studies were not designed to assess the safety of insulin, subjects could receive multiple glucose-lowering therapies, which makes individual comparisons difficult.

2.2.2.3. Randomised control trials and observational studies

2.2.2.3.1. Cardiovascular disease

In 2008, the FDA published guidance that recommended the inclusion of cardiovascular outcome trials when applying for a license for a glucose-lowering medication. The EMA produced their own guideline in 2012.[241] However, in a review of cardiovascular outcomes trials, Holman and colleagues suggested that many pharmaceutical manufacturers conduct non-inferiority, placebo-controlled trials, carried out with the minimum possible follow-up in order to show an absence of cardiovascular toxicity with the minimum risk and cost.[242] Therefore, at the time of licensing, the comparative effectiveness, long term safety, effects in patients with different clinical characteristics, and the risk benefit ratio of a glucose-lowering medication may not be fully understood.[242]

The University Group Diabetes Programme (UGDP) conducted in 1970 was a randomised controlled, multicentre, head-to-head effectiveness trial. Patients were

randomised to receive one of four glucose-lowering regimens: variable doses of insulin, standard dose of insulin, phenformin or tolbutamide and also placebo.[242,243] The study reported an increased cardiovascular risk for all therapies when compared with placebo.[242,243] Since its publications, the conduct of the UGDP has been heavily criticized.[244] However, although this study was underpowered with controversial findings,[244] it had far reaching consequences including to delay the introduction of metformin to the US market until 1994.[242]

In the first Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study, patients with diabetes who suffered an acute myocardial infarction were randomised to receive intensive insulin therapy or standard care following at least a 24 hour period standard treatment plus an insulin-glucose infusion.[245] Compared with standard care, insulin therapy was associated with an absolute reduction in mortality of 11%.[245] The recently published follow-up study (mean 7.3 years) found that intensive insulin therapy following acute myocardial infarction had a long –lasting effect on survival (HR 0.83, 95%CI 0.70–0.98).[246] The second DIGAMI study (DIGAMI 2) failed to reproduce the same results as the first study using a similar population. Patients with type 2 diabetes and a myocardial infarction were randomised to one of three treatment groups: group 1, acute insulin–glucose infusion followed by insulin-based long-term glucose control; group 2, insulin–glucose infusion followed by standard glucose control; and group 3, routine metabolic management according to local practice.[247] There were no significant differences in the risk of mortality between groups (HR 1.03, 95% CI 0.79–1.34, for group 1 versus group 2 and 1.23, 95% CI 0.89–1.69 for group 2 versus group 3).[247] However, less than half the number of planned participants were recruited to the study (1,253 instead of 3,000) and the predefined separation in glucose control between study arms was not

achieved.[247] In the post hoc analysis of the DIGAMI 2 study, insulin was associated with a statistically significant increase in non-fatal cardiac events[248] but was not associated with an increased risk of mortality (1.30, 0.93–1.81).[248] However, not all the baseline characteristics, which differed between groups, were included in the multivariate model.[248]

The results of ORIGIN, a large, multicentre RCT, have already been discussed previously (Chapter 2.2.2.2.4).

In the UKPDS, patients were randomised to intensive treatment with sulfonylureas or insulin or standard treatment with diet.[67] Insulin could be prescribed in combination with other glucose-lowering drugs with the aim of achieving a specific HbA_{1c} target. Therefore it is difficult to determine the effect of insulin on the study endpoints. However, unlike those patients receiving conventional glucose lowering treatment and sulfonylureas, patients treated with insulin experienced a sustained increase in plasma insulin levels.[67] Despite this, an excess of macrovascular outcomes was not observed in the intensively treated arm.[67] In addition, patients treated with insulin were not more at risk of myocardial infarction.[67] Other large RCTs such as ACCORD found no adverse safety signals associated with the use of insulin.[79] However, these studies were designed to assess the benefits of intensive glucose control rather than the safety of insulin, and subjects could receive multiple glucose-lowering therapies making individual comparisons difficult.

The multinational randomised controlled Hyperglycaemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus (HEART2D) trial compared prandial insulin with basal insulin in 1,115 people with type 2 diabetes following acute myocardial infarction.[249] The study found that

that there was no statistically significant difference in the composite endpoint of cardiovascular death, myocardial infarction, stroke, coronary revascularisation or hospitalisation for acute coronary syndrome between the treatment arms (HR= 1.04, 95% CI 0.78–1.37).[249]

The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) RCT compared insulin-sensitisation with insulin provision treatment in 2,368 people with type 2 diabetes and pre-existing heart disease.[250] After 5 years, there was no statistically significant difference in survival between treatment arms (88.2% versus 87.9%, respectively).[250] However, there was some crossover of therapies between study arms and HbA_{1c} levels were significantly lower in the insulin sensitisation group suggesting that either the insulin sensitising glucose-lowering medicines were more effective in terms of managing hyperglycaemia or the patients in the insulin provision group had more severe diabetes.[250]

Several observational studies have found an association between insulin use and the risk of serious cardiovascular events. A retrospective study conducted by Currie et al. using data from the General Practice Research database (GPRD) has shown that insulin treatment was associated with an increased risk of cardiovascular events (1.5 fold).[60] In a nested case-control study, Colayco and colleagues reported that insulin use was associated with a 2.5 fold increase in the risk of cardiovascular events when compared with no treatment with glucose-lowering therapy.[223] A separate retrospective observational study conducted by Currie and colleagues using data from CPRD found that relative to metformin monotherapy, insulin monotherapy was associated with an increased risk of MACE (HR 1.74, 95% CI 1.44–2.09).[61] However, when prescribed in combination with metformin, the risk associated with insulin was not statistically

significant (1.22, 95% CI 0.96–1.54).[61] Margolis and colleagues conducted a study using a different source of UK primary care data, The Health Improvement Network (THIN), and found that people with diabetes treated with insulin were at an increased risk of serious atherosclerotic disease of the heart (HR 1.2, 95% CI 1.1–1.3, for insulin; 1.03, 0.97–1.09, for sulfonylureas; 0.8, 0.7–0.8, for biguanide; 1.2, 0.99–1.5, for meglitinides; and 0.5, 0.5–0.6, for thiazolidinediones).[251] The risk of serious atherosclerotic disease increased with the duration of therapy for insulin, sulfonylureas, and biguanide, but decreased with duration for rosiglitazone and pioglitazone.[251] However, one study limitation is that patients with type 2 diabetes were not selected specifically. Ostgren and colleagues found that insulin treatment in type 2 diabetes was associated with an increased risk of a composite endpoint (first hospitalisation for acute myocardial infarction, heart failure, or stroke or cardiovascular mortality (aHR 1.36 95% CI 1.26–1.45) and cardiovascular death (1.46, 1.34–1.59) compared with treatment with oral glucose-lowering medication.[224] In a retrospective study conducted by Nichols and colleagues using data from the Kaiser Permanente Northwest diabetes registry, the addition of insulin therapy was associated with 2.33 and 2.66 times increase in the incidence of coronary heart failure in comparison to the addition of metformin or sulfonylurea, respectively.[252] Conversely, Hall and colleagues conducted a retrospective observational study using data from THIN and determined that the intensification of glucose-lowering therapy with insulin compared with other glucose-lowering medicines was only associated with an increased risk of macrovascular events in people who had previously received only one baseline treatment (aHR 0.53, 0.42–0.69, from one; 0.85, 0.70–1.04, from two; and 1.07, 0.50–2.30, from three baseline treatments).[253] The corresponding figures for microvascular disease were 1.01 (0.80–1.27), 0.99 (0.87–1.13) and 1.12 (1.67–2.07).[253] It was uncommon for people to start

insulin when receiving only one oral glucose-lowering medication and there were notable differences between the baseline characteristics of this group.[253] In a second study from the same research group, the risk of macrovascular events were similar when people previously receiving two or three glucose-lowering medicines were prescribed basal insulin compared to those prescribed pre-mix or NPH.[254]

An association between cumulative insulin exposure and risk of cardiovascular mortality was demonstrated by Gamble and colleagues in a retrospective study using data from Saskatchewan Health.[255] In the prospective observational Translating Research Into Action for Diabetes (TRIAD) study, insulin as monotherapy was associated with an increased risk of cardiovascular (aHR 1.55, 95% CI 1.19–2.01) and all-cause mortality (1.24, 1.05–1.46) in comparison with oral medication only.[256] However, no significant association was found for insulin in combination with oral therapy.[256] Anselmino and colleagues carried out an observational study of people with diabetes and coronary artery disease enrolled on the Euro Heart Survey of Diabetes and the Heart and found that people with known diabetes treated with insulin were associated with an increased risk of all-cause mortality after one year (aHR 2.23 95% CI 1.24–4.03).[257] However, no data was presented for people with type 2 diabetes specifically. Conversely, of the people with coronary artery disease that were newly diagnosed with diabetes, no people receiving glucose-lowering therapy died, compared with 22 patients receiving no glucose-lowering therapy (p=0.002).[257] In a retrospective study conducted using data from two Swedish registries with a mean follow-up time of 4.1 years, Saleh and colleagues found an increased risk of all-cause mortality in people with type 2 diabetes treated with insulin alone (HR 1.17, 95% CI 1.02–1.35) or in combination (1.22, 1.06–1.40) and undergoing coronary angioplasty when compared with diet alone.[258] Gu and colleagues conducted a study where insulin

naïve patients were recruited from the Shanghai Diabetes Registry and divided into an insulin group and a non-insulin group.[259] The risk for cardiovascular mortality was not found to be significantly higher for people using insulin (adjusted RR 1 83, 95% CI 0.91–3.68).[259] Khalangot and colleagues conducted a cohort study and reported an increased risk of cardiovascular mortality in people with type 2 diabetes treated with insulin when compared with oral glucose-lowering therapies (aHR 2.66, 95% CI 2.28–3.09, for insulin monotherapy and 2.51, 2.15–2.93, for insulin in combination with other glucose-lowering therapies).[260] In a small number of people with diabetes (type not specified) and advanced systolic heart failure, Smooke and colleagues found that insulin use was associated with an increased risk of mortality (HR 4.30, 95% CI 1.69–10.94) but non-insulin treated diabetes was not (0.95, 0.31–2.93).[261] Conversely, Masoudi and colleagues found no association between insulin use and mortality (aHR 0.96, 0.88–1.05) when compared with metformin, sulfonylureas, non-sulfonylurea secretagogues, thiazolidinediones or alpha-glycosidase inhibitors in people with diabetes and discharged from hospital with heart failure.[262] However, the authors did not present data for type 2 diabetes specifically.[262]

In a systematic review and meta-analysis conducted by Eurich and colleagues, the results of four studies comparing insulin use with other glucose-lowering therapies in people with diabetes and heart failure (2 studies provide adjusted estimates as described above[262,263] and two studies providing unadjusted estimates[261,264]) could not be pooled due to statistically significant heterogeneity between studies.[265]

2.2.2.3.2. Cancer

Recently, associations between glucose-lowering therapies (including insulin glargine, pioglitazone and incretin-based drugs) and an increased risk of cancer have received considerable attention.[266–269] In June 2009, the results of four epidemiological studies were published which suggested an increased risk of cancer and the use of insulin, particularly insulin glargine.[62,270–272] Several studies have since been carried out, including the large randomised control ORIGIN trial. ORIGIN found that that the use of insulin glargine in people with type 2 diabetes had no statistically significant impact on cancer risk.[80] However, this trial was powered to investigate cardiovascular outcomes rather than cancers. In addition, after six year, insulin doses remained relatively low (median 0.40, IQR 0.27–0.56 international units/kg).[80] In 2013, both the FDA and EMA determined that currently available data did not indicate an increased risk of cancer with insulin glargine.[273,274]

Meta-analyses investigating the association between insulin use and the risk of cancer in type 2 diabetes have been discussed previously (Chapter 2.2.2.2). In a more recent meta-analysis, insulin use was associated with an increased risk of lung cancer while no association was shown for thiazolidinediones and sulfonylureas.[275]

In a retrospective observational study using data from the UK CPRD, patients with type 2 diabetes treated with insulin were at increased risk of developing cancer when compared with metformin monotherapy (aHR 1.42, 95% CI 1.27–1.60).[62] In addition, people with insulin treated type 2 diabetes were at increased risk of mortality from these tumours compared with people without diabetes (aHR 1.13, 95% CI 1.01–1.27).[149] There is some evidence that the use of insulin may increase cancer risk in comparison with metformin[62,276,277] and other glucose lowering therapies.[278] Increasing

duration of insulin exposure has also been reported to be associated with an increased risk of colorectal cancer (adjusted OR 1.21, 95% CI 1.03–1.42, for each incremental year of insulin therapy).[278] One epidemiological study has also demonstrated a graded association between insulin exposure and death from cancer.[279] Gu and colleagues found that insulin use was associated with an increased risk of liver cancer (adjusted RR 2.84, 95% CI 1.12–7.17) and cancer-related mortality (2.16, 1.39–3.35) in a population of previously insulin-naïve patients from the Shanghai Diabetes Registry.[259] However, compared with no insulin use, insulin use was not associated with an increased risk of any incident cancer (1.20, 0.89–1.62).[259] In the Diabetes Cardiovascular Risk and Evaluation: Targets and Essential Data for Commitment if Treatment (DETECT) study, treatment with insulin as monotherapy or in combination with other glucose-lowering therapy in people with type 2 diabetes was associated with an increased risk of cancer related mortality when compared with people with no diabetes (aHR 3.96, 95% CI 1.82–8.63) whereas any glucose-lowering therapy other than insulin was not associated with a significantly increased risk (0.93, 0.41–.11).[280] In a retrospective study by van Staa and colleagues, it was reported that increases in cancer risk associated with insulin or sulfonylurea therapy could be explained by a protopathic bias and found no evidence that insulin increased the risk of cancer over time when compared with metformin.[281]

2.2.2.3.3. Microvascular

In the UKPDS, a reduction in microvascular complications (RR 0.70, 95% CI 0.52–0.93) and retinal photocoagulation (0.67, 95%CI 0.45–0.99) was observed in people with type 2 diabetes treated with insulin when compared with conventional therapy.[67] In a

RCT conducted in Japan, 110 patients were randomised to receive either multiple insulin injections or conventional insulin treatment.[282] Compared with convention insulin treatment, multiple insulin injection delayed the progression of retinopathy (7.7% versus 32.0%, p=0.039 in the primary prevention cohort and 19.2% versus 44.0%, p=0.049 in the secondary intervention cohort) and nephropathy (7.7% versus 28.0%, p=0.032, and 11.5% versus 32.0%, p=0.044) after six years.[282] However, this was a relatively small study where the study subjects were reasonably young and lean. [282] Conversely, in a prospective cohort study, starting insulin therapy in people with type 2 diabetes was reported to be related to worsening retinopathy.[283] However, it is unclear whether this is a causal effect or related to disease progression.[283] In a study by Arun and colleagues, it was hypothesised that the risk of exacerbating retinopathy after starting insulin may be lower than previously suggested.[284]

2.2.2.3.4. Other side effects

In addition to its link to cardiovascular risk, hypoglycaemia as a side effect of insulin therapy can cause significant morbidity[285] and has been tentatively linked to an increased risk of dementia.[286] Furthermore, insulin has been associated with an increased rate of fractures in people treated with insulin (OR 1.52, 95% CI 0.82–2.70) possibly due to an increased risk of falls.[287] Patients with hypoglycaemia are also likely to be less satisfied with their glucose-lowering therapy where hypoglycaemia is a barrier to treatment adherence.[288] In UKPDS, hypoglycaemia was highest in people treated with insulin (1.8% versus 1.0% and 1.4%, respectively).[67] Weight gain was higher with intensive treatment compared with conventional glycaemic control and people treated with insulin had a higher gain in weight compared with those treated

with chlorpropamide or glibenclamide (2.0kg versus 2.6kg and 1.7kg, respectively).[67] Weight gain and hypoglycaemia may counteract any quality of life benefits associated with improved glucose control.[289]

2.2.2.3.5. All-cause mortality

In a retrospective observational study using data from Saskatchewan Health, a significant, graded association between insulin and the risk of all-cause mortality was observed (aHR 1.75, 95% CI 1.24–2.47, for low exposure; 2.18, 1.82–2.60, for moderate exposure; and 2.79, 2.36–3.30, for high exposure).[255] In people identified from the Shanghai Diabetes Registry who were previously insulin-naïve, insulin use was associated with an increased risk of all-cause mortality compared with no-insulin use (adjusted RR 1.89, 95% CI 1.47–2.43).[259] Khalangot and colleagues found that insulin therapy was associated with an increased risk of all-cause mortality in people with type 2 diabetes compared with oral glucose-lowering agents (HR 2.34, 95% CI 2.13–2.57 and 2.12, 1.97–2.29, for insulin monotherapy and 2.22, 2.02–2.45, and 2.20, 2.04–2.37, for insulin plus metformin, for males and females, respectively).[260]

2.2.3. Financial cost

In 2013/2014, 6.5 million insulin items were dispensed on NHS prescriptions in England at a cost of £328.3 million.[290] Insulin accounts for 14.3% of all items prescribed for diabetes and 41% of the total cost. Injecting equipment (for example needles, syringes and pen devices) add to this cost. Since 2005/2006, the number of insulin items and their corresponding NIC has increased year on year in England.[290] Since their

introduction, the use of insulin analogues has increased steadily and they have had an increasing impact on the cost of prescribing for diabetes in the UK.[291] Insulin is a relatively expensive intervention, particularly when compared with generic glucose-lowering drugs.[47]

2.3. Influence of metformin on adverse events

Metformin was originally thought to be an insulin sensitizer.[115] However, metformin is now considered to suppress hepatic glucose production where activation of AMP-activated protein kinase may account for many of its effects.[292] Metformin has also been shown to induce GLP-1 secretion.[293] Metformin reduces hyperglycaemia and hyperinsulinaemia and is associated with weight loss.[115] Compared with a BMI of between 20 and 24, a BMI of greater than 30 has been found to be associated with an increased risk of all-cause mortality.[294] Furthermore, hypoglycaemia rarely occurs with metformin[295] and metformin may reduce oxidative stress.[115] Metformin has been shown to reduce the incidence of type 2 diabetes in people who at high risk of developing the condition.[121]

Metformin may indirectly lower the risk of cancer through the activation of AMP kinase causing the downregulation of key gluconeogenesis genes and the promotion of glucose uptake into muscle leading to a reduction in both plasma glucose and insulin levels.[81] Studies have shown that activation of AMP kinase by metformin causes a reduction in mammalian target of rapamycin (mTOR) signalling in cancer cells causing a reduction in protein synthesis and reduced proliferation of cancer cells.[81] Metformin may further protect against cancer through additional AMP kinase dependent and independent effects.[81]

In addition, results from UKPDS showed that metformin reduced the risk of all-cause mortality, diabetes-related mortality and myocardial infarction versus standard care even though patients in the metformin arm had a median HbA1c of 0.6% lower than standard care.[82] This suggests that metformin may have cardioprotective effects that cannot be fully explained by its ability to lower blood glucose. Improvement in endothelial dysfunction, may explain, at least in part, the reduced risk of cardiovascular disease associated with its use.[296–298] Furthermore, data from RCTs have shown that metformin is associated with improvements in body weight, lipids and blood pressure.[299,300] Metformin has also been shown to reduce plasminogen activated inhibitor-1, a risk factor for cardiovascular disease.[301]

Metformin is primarily eliminated by filtration and active tubular secretion in the kidneys.[302] Lactic acidosis is the most serious side effect associated with metformin treatment and metformin should be used with caution in people with renal impairment.[47] Phenformin, a biguanide and the predecessor of metformin, was withdrawn from US and European markets in 1977 due to the risk of lactic acidosis.[303] However, a recent Cochrane review found no cases of lactic acidosis in 70,490 patient-years of metformin use (and none in 55,451 patient-years for people not treated with metformin).[304] The low incidence of lactic acidosis observed may be due at least in part to the avoidance of metformin in high-risk groups. Nevertheless, when used appropriately, lactic acidosis associated with metformin use is likely to be a relatively rare event. Even when metformin is prescribed in situations where its use is contraindicated, it has been found to be relatively well tolerated.[305]

2.3.1. Glucose-lowering effect

Metformin is an effective glucose-lowering therapy and generally reduces fasting plasma blood glucose and HbA_{1c} in a dose related fashion.[306] A Cochrane review has demonstrated that metformin was associated with improved HbA_{1c}, fasting plasma glucose, low-density lipoprotein (LDL) cholesterol and triglyceride levels, and BMI when compared with sulfonylureas.[307] In the UKPDS, HbA_{1c} levels for patients assigned to intensive control with metformin were similar to those receiving intensive control using insulin or sulfonylurea during the 10-year follow-up.[82] In ADOPT (A Diabetes Outcome Progression Trial), the glycaemic durability of metformin was found to be greater than sulfonylureas but less than rosiglitazone.[308]

2.3.2. Cardiovascular

In the UKPDS study, a relatively small number of obese people with type 2 diabetes (bodyweight of more than 120% of the ideal) were randomised to receive either intensive glucose control using metformin (n=342) or conventional therapy (predominately diet alone, n=411).[82] A 33% (95% CI 13–47%) reduction in any diabetes related outcome, a 36% (95% CI 9–55%) reduction in all-cause mortality and a 42% (95% CI 9–63%) reduction in diabetes-related death with metformin treatment was reported.[82] A secondary analysis found that intensive glucose control with metformin was associated with a reduction in the risk of any diabetes related outcome, all-cause mortality or stroke when compared with intensive glucose control with insulin, glibenclamide or chlorpropamide.[82] The 10-year post-interventional monitoring programme showed a possible legacy effect for metformin (RR for any diabetes-related endpoint =21%, p=0.001; myocardial infarction =33%, p=0.005; and all-cause

mortality =27%, p=0.002).[112] In the absence of other RCT data, considerable emphasis is placed on the results of the UKPDS when recommending the use of metformin in prescribing guidelines. Counter intuitively, UKPDS 34 also reported an increased risk of diabetes related deaths (1.96, 1.02–3.75) and all-cause mortality (1.60, 1.02–2.52) with metformin and sulfonylurea combination therapy when compared with continued sulfonylurea monotherapy alone.[82] However, only a small number of events were observed.

In a meta-analysis of RCTs, Boussageon and colleagues found that the use of metformin did not significantly affect the risk of all-cause mortality (RR 0.99, 95% CI 0.75–1.31), cardiovascular mortality (1.05, 0.67–1.64), myocardial infarction (0.90, 0.74–1.09), strokes (0.76 0.51–1.14), heart failure (1.03, 0.67–1.59), peripheral vascular disease (0.90, 0.46–1.78), leg amputations (1.04, 0.44–2.44) and microvascular complications (0.83, 0.59–1.17).[309] However significant heterogeneity was observed for all-cause and cardiovascular related mortality due to the inclusion of the two UKPDS metformin studies.[309] A meta-analysis by Stevens and colleagues did not report a significant reduction in all-cause mortality with metformin (RR 0.94, 95% CI 0.79–1.12).[310] However, heterogeneous comparator types and short follow-up were limitations of this meta-analysis.[310] In a meta-analysis of patients with diabetes and heart failure, metformin was associated with a significant reduction in all-cause mortality in two studies (HR 0.86, 95% CI 0.78–0.97 when compared with other glucose-lowering therapies including insulin and 0.70, 0.54–0.91 when compared with sulfonylureas) and a similar trend was observed in a third study.[265] Metformin was the only glucose-lowering therapy not associated with harm in patients with heart failure and diabetes.[265] In a meta-analysis of 35 RCTs, metformin was found to significantly

reduce cardiovascular risk versus placebo or no therapy (MH-OR 0.79, 95% CI 0.64–0.98) but no significant effect versus active comparators (1.03, 0.72–1.77).[311]

Several observational studies have demonstrated an increased risk of cardiovascular events[61,312–314] and cardiovascular deaths[315] when sulfonylurea monotherapy was compared with metformin monotherapy. A randomised, double-blind, placebo-controlled trial showed that the risk of cardiovascular events in people with type 2 diabetes and a history of coronary heart disease was lower for metformin than for glipizide (aHR 0.54; 95% CI 0.30–0.90).[316] A meta-analysis of clinical and observational studies by Phung and colleagues found that relative to metformin, the risk associated with sulfonylureas was 1.26 (95% CI 1.17–1.35) and 1.18 (1.13–1.24) for cardiovascular death and cardiovascular events, respectively.[317] Selvin and colleagues showed that the risk of cardiovascular mortality was lower for metformin than any other comparator (OR 0.74, 95% CI 0.62-0.89) but that the risk for sulfonylurea was not significantly different to other comparators (OR 0.92, 95% CI 0.68-1.26).[318] In a meta-analysis consisting predominately of observational studies only, Eurich and colleagues found that people with heart failure treated with metformin had a 20% lower mortality rate compared with the control group who were predominately treated with sulfonylureas, and no increased risk of lactic acidosis was observed in the metformin treated subjects.[319] In a retrospective cohort study, high dose metformin was not associated with an increased risk of developing heart failure versus low dose metformin (HR 1.06, 95% CI 0.81–1.41).[320] Patients with established atherothrombosis and diabetes participating the Reduction of Atherothrombosis for Continued Health (REACH) registry and treated with metformin, had a lower risk of mortality versus no metformin use (aHR 0.76, 95% CI 0.65–0.89).[321] Danish patients with type 2 diabetes treated with metformin in the 90 days following hospital admission with a myocardial

infarction had a similar risk of death, a further myocardial infarction and heart failure in the first year following the event as patients treated with sulfonylureas (aHR 0.96, 95% CI 0.71–1.31; 1.21, 0.77–1.92; and 0.81, 0.51–1.29, respectively).[322] Conversely, a meta-analysis by Monami and colleagues also found no statistically significant difference in the risk of death from all-causes for sulfonylureas compared with metformin (OR 1.29, 95% CI 0.80–2.13).[226] In addition, the randomised double-blind controlled trial ADOPT showed that glibenclamide was associated with a lower risk of cardiovascular events when compared with rosiglitazone, and that metformin was associated with a similar risk to rosiglitazone. However, this study was not designed to evaluate cardiovascular outcomes.[308]

2.3.3. Cancer

A meta-analysis and systematic review of epidemiological studies by Decensi and colleagues found that the risk of cancer in people with diabetes treated with metformin was 31% lower than those treated with other glucose-lowering therapies.[323] People with type 2 diabetes treated with metformin have been shown to have reduced risk of cancer compared to the general population.[149] The Zwolle Outpatient Diabetes project Integrating Available Care (ZODIAC) study in the Netherlands found that increasing metformin dose was associated with a reduction in the risk of cancer (aHR 0.58, 0.36–0.93 for every 1g increase of metformin dose).[324]

One observational study utilising data from CPRD found that there was no significant difference in the risk of malignant solid tumours and haematological malignancies when comparing sulfonylureas with metformin (aHR 1.06; 95% CI 0.98–1.15 and 0.98; 0.67–1.43, respectively).[325] However, other observational data[61,62,326,327] and meta-

analyses[328,329] support the thesis that metformin is associated with a reduced risk of cancer in comparison with sulfonylurea monotherapy and insulin monotherapy .

Conversely, the results seen for metformin in the meta-analyses of observational studies have not been replicated in the meta-analyses of RCTs. A recent Cochrane meta-analysis combining data from RCTs did not find any significant beneficial effects of metformin on cancer [231]. The confidence intervals calculated were broad but the authors concluded that even if a beneficial effect of metformin on cancer exists, it is likely to be smaller than estimated from observational data [231]. Stevens and colleagues, found that when data from RCTs was combined, metformin only reduced the risk of cancer versus placebo or usual care (RR 1.36, 95% CI 0.74–2.49) and not versus active comparators (0.98, 95% CI 0.77–1.23).[310]

In terms of site-specific cancers, metformin has been associated with a decreased risk in lung cancer in people with diabetes but this effect was not significant when only those studies that adjusted for smoking status were analysed.[275] In two meta-analyses metformin use was associated with a significant (RR 0.63, 95% CI 0.50–0.79)[330] and non-significant reduction (OR 0.75, 95% CI 0.43–1.31)[233] in the risk of colorectal cancer. In meta-analyses conducted by Zhang and colleagues, metformin use in type 2 diabetes was associated with a significant reduction in liver cancer (OR 0.38, 95% CI 0.24–0.59) and hepatocellular carcinoma (OR 0.30, 0.17–0.52), however, there was some heterogeneity across studies.[331,332] Several meta-analyses have been carried out investigating the association between glucose-lowering therapies and the risk of breast cancer in postmenopausal women with both significant reductions [333] and non-significant associations [328] reported for metformin. One meta-analysis did not find a

significant association between the risk of prostate cancer and the use of metformin.[328]

In terms of survival following cancer diagnosis, mixed results for the effect of metformin have been observed. No association was found between cumulative metformin duration and survival in older people with recent onset diabetes following diagnosis of breast cancer.[334] In addition, in a retrospective observational study, Bayraktar et al found that metformin use during adjuvant chemotherapy had no effect on survival in patients with triple receptor negative breast cancer and diabetes.[335] However, people with human epidermal growth factor receptor 2 positive (HER2+) breast cancer and diabetes had improved survival if they were receiving a thiazolidinedione or metformin as glucose-lowering therapy when compared with people with diabetes who did not receive these medicines.[336] An association between metformin use and survival following diagnosis with colorectal cancer in people with diabetes has been demonstrated in a meta-analysis by Mei and colleagues.[337] Improved survival has also been reported for the use of metformin in people with ovarian cancer in a separate meta-analysis by Kumar and colleagues (HR 2.2, 95% CI 1.2–3.8).[338]

2.3.4. All-cause mortality

The UKPDS found that overweight patients receiving intensive treatment with metformin monotherapy had a lower risk of any diabetes-related endpoint, stroke or all-cause mortality when compared with intensive treatment with insulin or sulfonylureas.[82] Retrospective observational studies using the CPRD have reported that, compared with metformin monotherapy, sulfonylurea monotherapy was

associated with an increased risk of all-cause mortality in type 2 diabetes.[61,312] A retrospective cohort analysis using the Saskatchewan Health Administrative Databases in Canada found that, relative to sulfonylurea monotherapy, metformin monotherapy was associated with a lower risk of a composite endpoint defined as the first non-fatal hospitalisation or death (aHR 0.81; 0.68–0.97).[339] Other observational data comparing sulfonylureas with metformin have also supported the observation that sulfonylureas are associated with a higher risk of mortality as a class,[315,340,341] and glipizide, glimepiride, tolbutamide and glibenclamide specifically.[342] Conversely, a retrospective study using data from Veterans Health Administration Diabetes Epidemiology Cohort found that the risk of all-cause mortality was not significantly different for metformin monotherapy and sulfonylurea monotherapy (adjusted OR 0.87, 95% CI 0.68–1.10).[343] In addition, a meta-analysis of available RCT data did not find that metformin had a statistically significant effect on all-cause mortality.[310] However, as the authors concluded, short follow-up time (average 2.8 years) was a limitation of their meta-analysis.[310]

2.3.5. The concomitant use of metformin in people with type 2 diabetes treated with insulin

Current ADA/EASD and IDF guidelines advocate that when starting insulin, it should be added to existing metformin therapy and not replace it.[7] NICE recommends that insulin is added to existing metformin plus sulfonylurea treatment.[55]

When used in conjunction with insulin, metformin has been associated with similar glucose control, but lower insulin doses and less weight gain.[83] Results from a randomised trial of 58 patients with newly diagnosed type 2 diabetes showed that

HbA_{1c}, weight gain and the number of hypoglycaemic events were similar for insulin plus metformin and triple therapy with metformin, pioglitazone and glibenclamide at 3 years.[344]

In addition, relative to the use of insulin alone, the use of metformin in combination with insulin has been associated with a reduced risk of cardiovascular events, cancer and death from any cause.[61,62,345] Conversely, in a recent retrospective cohort study using data from the Veterans Health Administration, Medicare, and National Death Index databases, people who were initially treated with metformin and subsequently added either insulin or sulfonylurea were matched in a ratio of 1:5 using propensity score matching.[346] Compared with adding a sulfonylurea to existing metformin therapy, the addition of insulin was found to be associated with an increased risk of a composite of non-fatal cardiovascular outcomes and all-cause mortality (aHR 1.30; 95% CI 1.07–1.58; p=0.009).[346]

2.4. Summary

In terms of reducing cardiovascular risk, adequate control of blood pressure and lipids should be emphasised because they have been shown to play a more important role in terms of coronary heart disease and stroke prevention in comparison with blood glucose.[347]

Many of the large RCTs have focussed on intensive versus convention glycaemic control rather than the comparison between different glucose-lowering drugs. ORIGIN is an exception to this and selected people with type 2 diabetes and a prior history of cardiovascular disease. Due to its size and length of follow-up, ORIGIN provides

important data on the effect of insulin glargine on the risk of cardiovascular outcomes. However, the patients selected had low HbA_{1c} levels at baseline and were not generally representative of people who receive insulin in type 2 diabetes in the real world.[80] There is a possible argument that the results of the observational studies may be due to residual confounding and it is difficult to fully remove this bias. Therefore, it is difficult to confirm or disprove any associations between insulin and cardiovascular risk from these studies alone. For example, insulin is more frequently prescribed to people with a longer duration of diabetes and more comorbid conditions.[84]

There are several difficulties associated with carrying out and interpreting research studying possible associations between glucose-lowering therapies and cancer and cardiovascular events. It is common for patients to receive a combination of two or more medications for lowering blood-glucose, which can complicate investigations into the effect of individual glucose-lowering agents on cardiovascular or cancer risk. For example, in the ORIGIN trial, 11% of the standard group received insulin therapy and 46.5% of the insulin glargine group also received metformin.[80] In addition, cancer can typically take several years to develop, therefore adequate length of follow-up is required. Furthermore, when comparing two or more glucose-lowering therapies, it is difficult to know whether any increased risk associated with one agent is due to detrimental effects associated with the agent or positive effects associated with the active comparator.

Due to the prevalence of diabetes, even a small increase in risk of cancer or cardiovascular disease in people with type 2 diabetes still has the potential to affect a large number of people at the population level. Appropriate management of type 2 diabetes is required in order to minimise the risk of morbidity and mortality that is

associated with this condition. Here we have discussed the current literature investigating the relative risks and benefits associated with exogenous insulin. However, any potential risks associated with insulin therapy need to be seen in the context of the need to achieve good glucose control. For example, insulin is necessary for all people with type 1 diabetes and also some people with type 2 diabetes where management of hyperglycaemia resulting from progressive loss of beta cell function is required.[84] In a review of the current evidence, the ADA and the American Cancer Society concluded that the risk of developing cancer should not play a major role in the selection of glucose-lowering medication for the management of type 2 diabetes but could be a consideration for people with a high risk of cancer occurrence or recurrence.[84] However, the adoption of a healthy lifestyle including increased physical activity and weight management may lead to improved outcomes for people with type 2 diabetes.[84]

Diabetes is a complex disease where both risk factors associated with the condition, complications arising from the condition and the management of the condition can play an important role in the risk of cardiovascular events, cancer or death. ORIGIN provided some reassurance for the use of insulin in type 2 diabetes however, it was not specifically designed to investigate the safety of insulin. In the absence of further RCTs, well designed observational studies could provide more information on the safety of insulin in type 2 diabetes.

3. Overview of methods and datasets

This thesis comprises a series of retrospective observational studies using data from CPRD and the Prescription Cost Analysis (PCA). This chapter discusses the advantages and disadvantages of the study design. In addition, the general methods and data sources used for this series of retrospective studies are described and discussed. However, the study methodology has been adapted to suit each study individually and is described in detail in each Chapter.

3.1. Advantages and disadvantages of retrospective observational studies

In terms of evidence based medicine, randomised, controlled trials (RCTs) and systematic reviews of RCTs occupy the highest levels in the hierarchy of evidence, whereas clinical observation and expert opinion occupy the lowest levels. Retrospective observational studies are found at an intermediate level.[348] In 2011, the Oxford Centre for Evidence Medicine devised Levels of Evidence to replace the hierarchy following criticism of inflexibility in the use of the hierarchy.[225] Observational studies are ranked at various levels in this table depending on the research question and the quality of the research.[225]

Retrospective observational studies have numerous advantages. They are considerably cheaper to carry out than prospective studies and RCTs and samples sizes can be large. This facilitates the study of less common diseases. Data have already been collected therefore studies can be quick to carry out and long length of follow-up allows retrospective studies to be conducted for diseases with long latency periods. Risk

factors are recorded prior to the occurrence of outcome reducing bias. Multiple outcomes can also be examined in a single study. RCTs may have ethical implications e.g. when a treatment is withheld or an inferior treatment is given. Retrospective observational studies do not have these considerations. Recent literature has shown that observational studies and RCTs produce comparable results.[349,350] Conversely, Ioannidis et al. found that differences in the estimated magnitude of treatment effects between randomised and non-randomised studies are common but there was good correlation between study types.[240] Retrospective studies can be used to investigate rates of disease over time[351] and data can be collected in a standardised way to allow comparisons to be made over time. The population studied may be more generalizable to the whole population and more likely to reflect general clinical practice than RCTs which often apply strict selection criteria.[352] In addition, RCTs contain only those patients who have actively signed up for the study. Retrospective observational studies do not require individual patient consent, therefore this type of selection bias is avoided.[352] In addition, the research question is unknown at the time data is collected therefore observer bias will be reduced.

Retrospective observational studies are also associated with some disadvantages. Depending on the data source, there can be a cost for acquiring the data (e.g. CPRD). Patients are not randomised, therefore there is the potential for a type of bias known as confounding by indication, where the outcome may be related to the reason a treatment was selected for the patient and not the treatment itself. Statistical methods can be used to correct for known confounders, however unknown confounders cannot be accounted for.[353] Therefore, retrospective observational studies generally can only demonstrate associations whereas cause and effect should be ideally measured using RCTs. However Sir Austin Bradford Hill listed certain criteria

which, if met, could allow causation to be inferred between a risk factor and an outcome in observational studies.[354] Depending on the data source, data may be collected for a purpose other than research and the researcher has limited or no control over data collection. Therefore, data may be incomplete, inconsistently recorded or inaccurate.[351] In addition, missing data may not be missing completely at random. Observational studies do not automatically control for selection bias. Consequently statistical methods are required to overcome differences in baseline characteristics, e.g. matching, co-variance adjustment or stratification.[352] Bias can also occur if the sample studied is not representative of the population as a whole. Unlike RCTs, blinding cannot be achieved using retrospective observational data. Patients and physicians and those assessing the outcome are aware of the nature of the treatment prescribed.

The advantages and disadvantages relating to CPRD and PCA specifically are described in detail in sections 2.21 and 2.22.

3.2. Data sources

3.2.1. Clinical Practice Research Datalink (CPRD)

3.2.1.1. History

The data source used for this series of studies was CPRD.[355] The database was established as a commercial venture in 1987 and was known as Value Added Medicinal Products (VAMP).[356,357] In addition to providing a tool to allow general practitioners (GPs) to record relevant clinical information, data was also anonymised and used for public health research. In 1993, VAMP Ltd. was acquired by Reuters who subsequently

donated the database to the Department of Health in 1994 and the database was renamed as GPRD and operated on a not-for-profit basis.[356] Under the control of the Medicines and Healthcare products Regulatory Agency (MHRA), the database was further renamed in 2012 and is now known as CPRD.[358] The aim of CPRD is to combine the expertise of GPRD and the Department of Health's National Institute for Health Research (NIHR) Research Capability Programme in order to enable researchers to utilise the power of large linked datasets.[358] To date, more than 800 scientific articles based on CPRD and its predecessors have been published.[359] In addition, numerous papers have been published that have utilised CPRD to study type 2 diabetes.[360]

3.2.1.2. Description of the database

CPRD's primary care dataset is called CPRD GP Online Data (GOLD). CPRD GOLD contains clinically rich, pseudonymised data collected in a non-interventional manner from the daily record-keeping of primary-care physicians in the UK. The following patient information is recorded by GPs using the Vision software and is therefore available in CPRD GOLD:

- Patient demographics (for confidentiality reasons, patients are attributed a unique patient identifier and only their year of birth is provided)
- Signs, symptoms and diagnoses (recorded using Read codes)
- Primary care prescriptions for medicines and devices
- Immunisations
- Results of investigations
- Referrals to specialists and secondary care
- Feedback from other care settings e.g. discharge summaries

- Lifestyle information such as BMI, smoking, alcohol consumption and exercise

By September 2013, CPRD GOLD contained over 13 million research quality patients registered at 678 GP practices.

3.2.1.3. Structure of the database

The data was provided by CPRD as flat text files and included the following data files:

- Practice details
- Patient details
- Consultations
- Staff
- Clinical
- Therapy
- Referrals
- Tests
- Immunisations

Data files are linked by a unique individual patient identifier.

3.2.1.4. Data linkages

For a proportion of English practices, primary care records have been linked to the NHS Hospital Episode Statistics (HES) data set.[361] As a result, details of inpatient admissions are also provided for those patients with a linked HES record. Diagnostic data in HES are recorded as International Classification of Diseases ICD-10 codes. Although only

linked HES data has been utilised in this series of studies, the following linked datasets are also available:

- Death data from Office for National Statistics (ONS) mortality data
- Cancer registry data from the National Cancer Intelligence Network (NCIN)
- Cardiovascular registry data from the Myocardial Ischaemia National Audit Project (MINAP)
- Socioeconomic data from the patient Lower Super Output Area (LSOA)[361]

Patient characteristics have been shown to be similar in linked and unlinked practices.[362]

3.2.1.5. Strengths and weaknesses

CPRD GOLD data are collected in all four UK regions (England, Scotland Northern Ireland and Wales) and is representative of the population in terms of crude mortality.[363,364] However, age-standardised mortality rates are 9–13% lower than the national average, which has been attributed to a healthy user bias and the exclusion of people with no exact date of death.[364] The age and gender structure of CPRD GOLD is similar to the UK population but the size of registered practices are larger than average.[364,365] In addition, CPRD contains a higher proportion of people living in Scotland, Wales and Northern Ireland and a smaller proportion of people living in England when compared with the UK population.[365] CPRD GOLD is also a very large longitudinal dataset which allows even relatively rare conditions to be studied with adequate statistical power.[366] Khan and colleagues conducted a systematic review for 40 papers investigating the validity of diagnostic coding in GPRD and reported that the positive predictive value for most conditions investigated was more than 50% and 14

of the conditions investigated had a positive predictive value of more than 90%.[367] However, rates of diabetes and musculoskeletal conditions were underestimated in GPRD.[367] In a more recently conducted systematic review by Herrett and colleagues, 212 papers, each validating at least one diagnosis, were identified and the median proportion of cases with a confirmed diagnosis was 89% (range 24–100%).[368] Furthermore, Jick and colleagues evaluated 58 practices and found that 87% of patients who had a clinical diagnosis recorded in a consultant letter kept in general practitioners' files also had a recorded diagnosis within their computer record.[369] A follow-up study evaluated a further 35 practices and reported that the information in consultant letters was recorded on the computer in 96% of instances.[370]

Prescriptions are generally computer generated and recorded simultaneously, improving the quality of the prescription data stored in the therapy table in CPRD.

On receipt of the data from the contributing practices, the data is checked to ensure it is of adequate quality. However, as an observational dataset, the quality of the data in CPRD GOLD is reliant upon the accuracy of the data inputted at practice level. Therefore recording guidelines are provided to contributing practices to ensure that the data quality is as high as possible.[361] In addition, once the data has been uploaded to CPRD, reports are sent to the practices to provide feedback.[356] Inconsistencies and deficiencies are highlighted by CPRD and instructions and support are provided in order to help correct any issues.[361] If these issues are not addressed by the practice, their data are no longer included in the dataset.[361] In addition, data of questionable quality is flagged so that it is easily identifiable to the researcher.[361]

The quality of the data stored in CPRD GOLD has improved over time. In particular, the introduction of the QOF as part of the new General Medical Services (GMS) Contract

on 1st April 2004[371] has led to an improvement in data recording at practice level across the UK.[372] QOF has incentivised practices to achieve high standards of data recording. The proposed implementation of a single linked NHS computer system of electronic patient health records (National Programme for Information Technology, NPfIT) may also encourage improved data completeness.[372]

CPRD utilises a process that identifies patients who have non-continuous follow-up or poor data quality.[356,361] Patients are identified as unacceptable if they meet one or more of the criteria described in Table 3.1.[356,359,361] Patients without these issues are of satisfactory research quality and are flagged as acceptable in the database and account for approximately 88% of patients.[359]

Table 3.1 Criteria implemented by CPRD to flag patients as unacceptable

Data item	Unacceptable value
First registration date	Empty or invalid
	Prior to year of birth
Year of birth	Missing
Transferred out reason	Missing
Transferred out date	Missing
	Prior to first registration date
	Prior to current registration date
Current registration date	Prior to first registration date
	Prior to year of birth
Gender	Not recorded as male, female or indeterminate
Age	>115 years at end of follow-up
Healthcare episodes	Records prior to year of birth
Registration status	Temporary

The overall quality of the data from contributing practices is also evaluated to ensure adequate continuity in data recording and avoidance of the use of data for which transferred out and dead patients have been removed.[359,361] For practices whose data is an acceptable quality, an up-to-standard date is applied. This date corresponds to the date at which the practice is considered to have been supplying continuous high quality data suitable for research use and is updated each time the practice contributes new data to the database.[361]

Data is continually being collected and added to CPRD GOLD and therefore the data used for this series of studies is up to date. Also as data continues to be collected, the database can be used to assess trends over time by the repeat application of the same methods.

Although CPRD GOLD is a primary care database, due to the role of the GP in the NHS, some secondary data is still recorded. In the UK the GP acts as a gatekeeper and refers patients to specialist or secondary care when necessary and receives feedback in the form of discharge summaries and outpatient letters from secondary care. This information is recorded in CPRD GOLD. However, prior to 2002, communication from secondary care and test results were not received electronically and had to be entered onto the computer manually.[366] Therefore, information before this date may not be complete.

Data are recorded by the GP routinely as part of the normal course of care where the aim of the GP is not to produce a complete database resource for public health research but to record the information that in his or her opinion is important in terms of the overall on-going clinical care of the patient. For example, a GP may be more

likely to record a patient's weight if they are obese and suffering from type 2 diabetes than if they were of normal weight and healthy.

CPRD GOLD will not contain any data for prescriptions issued in secondary care or records for the purchase of over the counter medicines. Therefore, information on medications prescribed exclusively in secondary care may be sparse. In addition prescriptions recorded in the therapy table in CPRD only indicate what has been prescribed to a patient and not what has been dispensed and consumed by the patient. In addition, CPRD GOLD does not routinely contain information on occupation, employment and socioeconomic status (except in the linked datasets).[366]

Although a patient may have a follow-up period from the start of the database in 1987 to the present day, this unlikely to be the case for the majority of patients due to a propensity for patients to change practice and the high turnover of participating practices during the lifetime of the database.

A recent systematic review by Herrett and colleagues reported on 357 validations of 183 different diagnoses.[368] However, there are still many diagnoses that have not been verified. In addition, diagnoses for conditions that have occurred prior to a patient's CPRD registration date may not be present if they are no longer suffering from the condition.[366] GPs have the option of recording uncoded comments as free text but this data is not routinely provided as part of the CPRD GOLD dataset. These free text fields could contain information from hospital discharge summaries, outpatient letters or more information on symptoms and diagnoses. However, analysing free text fields can be challenging and obtaining this data incurs an extra financial cost.

3.2.1.6. Ethical approval

GPRD was granted a blanket ethical approval by the Multicentre Research Ethics Committee (MREC) in 2006 for studies that are purely observational in nature. This approval has since been extended to cover observational studies utilising external data linkages with e.g. HES. However, study protocols need to be submitted to and approved by the Independent Scientific Advisory Committee (ISAC) if results are to be published or disseminated to a third party.

3.2.1.7. Data management

Sara Jenkins-Jones is the data manager for the CPRD flat files and administers the linked CPRD primary care and HES data sets. She has created procedures to clean and dimensionalize the data for high-performance access, and bespoke tools to facilitate analysis and improve reproducibility.

3.2.1.8. Selection criteria

Despite the advantages of using CPRD GOLD as a data source, the selection of people with type 2 diabetes in CPRD is challenging due to the presence of non-specific diagnosis codes, conflicting diagnoses, diagnoses that conflict with prescribed glucose-lowering therapies and also missing diagnoses or prescription history.

For this series of retrospective cohort studies, a series of decision rules will be implemented in order to select diabetes cases. These decision rules are based on a combination of both prescription history and diagnoses. The diagnoses were taken from the clinical table and HES, which are the more reliable sources in CPRD. Where

applicable, a wash-in was applied to ensure that only incident cases were selected and followed-up. The wash-in was applied to the later of a patient's current registration date or the practice up-to-standard date and only acceptable patients were used in order to ensure that the standard of the data used was as high as possible.

Each study required different selection criteria depending on the study aim. For example, studies investigating a possible association between insulin exposure and the risk of all-cause mortality, MACE and cancer in people with type 2 diabetes require relatively strict criteria for the selection of cases in order to have the best certainty that the cases selected have the condition you wish to investigate. CPRD GOLD is a large database and therefore the loss of some cases that are more uncertain would still allow sufficient power for detecting the association. For prevalence and incidence studies, the study criteria may be more relaxed to ensure a more accurate estimate of the epidemiology of diabetes in the general population. However, even then, the selection criteria can vary between studies. For example, the prevalence of insulin use and prevalence of diabetes studies had two different starting points. The prevalence of insulin studies started by selecting people with insulin prescriptions and then categorised these patients where possible into people with type 1 and type 2 diabetes. The prevalence of diabetes study however first selected people with diabetes.

3.2.1.9. Definition of drug exposure

CohortGenerator is an in-house software application developed by Sara Jenkins-Jones and was used to determine the periods of exposure to one or more glucose-lowering therapies for this series of studies. It is useful for cohort studies with complex drug histories where glucose-lowering agents including insulin can be used singly or in

combination, which frequently occurs in the management of type 2 diabetes. The software application allows the composition and duration of combination therapies to be determined by identifying cohesive, overlapping periods for the component drugs. Combination therapies were identified using an algorithm that identifies the first therapy (in start date order) and any augmenting therapy (a therapy with a start date within the duration of the first therapy). In order to be classed as a combination therapy, the component therapies must overlap by a period defined as the shorter of 30 days or the average interval between that patient's prescriptions for those therapies. The start of the combination therapy was taken as the start date of the augmenting therapy. The end of the combination therapy exposure period was defined as the earlier of the last prescription dates for the component therapies. Each patient's prescription history was therefore resolved into a sequence of discrete monotherapies or combination therapies of interest and assigned a quality score based on duration, prescription frequency, gaps in the prescription history, and the ratios of prescriptions for each component in a combination therapy.

3.2.1.10. Definition of baseline characteristics and model covariates

3.2.1.10.1. Duration of diabetes

The true duration of type 2 diabetes cannot be determined from CPRD GOLD as the symptoms of type 2 diabetes can be mild, especially in the initial stages, and the condition can remain undiagnosed for several years.[17] Therefore the duration of diagnosed diabetes was used as an estimation of the degree of disease severity. The duration of diagnosed diabetes at baseline was calculated as the number of days between the diabetes presentation date and the study index date. The diabetes

presentation date is defined as the earlier of the first recorded diabetes diagnosis or the first prescription for a glucose-lowering therapy.

3.2.1.10.2. Smoking status

Subjects were characterised as current smokers, ex-smokers or non-smokers. The most recently recorded smoking status prior to index date was used. As part of the data cleaning process when a new cut of data is received from CPRD, people who have previously been recorded as a current smoker and then subsequently received a code for a non-smoker are characterised as an ex-smoker.

In a validation study carried out by Booth and colleagues, the prevalence of smoking and non-smoking estimated using data from CPRD has been shown to be similar to that reported by the Health Survey For England 2007 to 2011, whereas the prevalence of former smoking was found to be underestimated in CPRD.[373]

3.2.1.10.3. Comorbidity

Several measures of comorbidity were used as covariates in the extended Cox model. The Charlson comorbidity index is a weighted index devised to take into account the number and severity of comorbid conditions that may influence the risk of all-cause mortality.[374] The number of GP contacts recorded in the year prior was used as an alternative measure of comorbidity.

A history of comorbid conditions including prior cancer or cardiovascular disease and a history of concomitant medications suggestive of cardiovascular disease were also used as covariates in survival modelling. A diagnosis of cancer or cardiovascular

disease or a prescription for antiplatelet, antihypertensive or lipid-lowering therapy recorded prior to the index date was used to identify a prior history of these conditions or concomitant medications.

3.2.1.10.4. Test results

HbA_{1c}, as a measure of glucose control, was used as a covariate in the survival models. HbA_{1c} results were identified for the study population from the test table. HbA_{1c} at baseline was defined as the nearest record within 365 days before and 30 days after insulin initiation, searching in the following order 30 days prior, 30 days after then 365 days prior to the index date. BMI, baseline serum creatinine, systolic blood pressure and total cholesterol were identified using the same search criteria.

3.2.1.11. Clinical endpoints

All-cause mortality, cancer and MACE were used as endpoints. For all-cause mortality, patients were followed up from their index date to their date of death as recorded in the currently held with a patient's registration details in CPRD. MACE was defined as myocardial infarction, stroke or cardiovascular death and patients were followed up from their index date to the date of their first event of interest. Cancer was defined as all cancers except for non-melanoma skin cancer.

3.2.2. Prescription cost analyses

3.2.2.1. Description of the data

The PCA provides details on the number and cost of items dispensed by community pharmacies, appliance contractors and dispensing doctors and submitted to the relevant authority for pricing and reimbursement. They are published for each region of the UK (England,[375] Northern Ireland,[376] Scotland,[377] and Wales[378]) . Although, the data reported relates to the prescriptions dispensed by community pharmacies within that region and not to the location of the GP practice. The PCA includes dental, hospital, nurse and prison prescriptions dispensed in the community but items dispensed by hospitals or prisons are not included. The data relates to NHS prescriptions only, therefore private prescriptions are also not included. PCAs are published at intervals varying from monthly to yearly. Although there are some variations in the information provided by each region and over time, each region provides data for individual preparations, which are then categorised using the BNF hierarchy.

3.2.2.2. Strengths and weaknesses

The PCA can be used to detect trends over time provided the rate of inflation is adequately accounted for. In addition, the PCA is available for all four regions of the UK and has good coverage for GP practices. Once the data from the four regions has been combined, prescriptions issued in one region and dispensed in another will still be captured.

However, the PCA does not include prescriptions dispensed in hospital and is therefore not suitable for some medications that are largely dispensed in hospital pharmacies,

e.g. biologics and chemotherapy. Patient level data is also not provided. In addition the period of time covered by each dataset varies by UK region, Scotland provides data by financial year and Wales and Northern Ireland provides data by calendar year.

3.2.2.3. Data management

For each individual PCA dataset (for a given time period and UK region), the headings of the columns were standardised. This included the standardization of the units (some PCAs reported their figures in thousands and others in individual units). The individual datasets were then combined using Microsoft Access to provide data for all four regions of the UK for the duration of the study period.

3.2.3. Population estimates from the Office for National Statistics

Population estimates are compiled by the ONS.[379] Estimates are based on the resident population of the UK and are provided by year of age, gender and region of the UK. The estimates are developed using several data sources and statistical models.[379] The mid-year estimates refer to the size of the population on the 30th June each year.[379] ONS produces estimates for England and Wales. The National Records of Scotland (NRS) and Northern Ireland Statistics & Research Agency (NISRA) produce estimates for Scotland and Northern Ireland, respectively. ONS then compiles and publishes the estimates for the UK as a whole.[379]

3.2.3.1. Strengths and weaknesses

Data are free to access and are available for each UK region. Estimates are provided by age and gender, which are useful to allow multiplication by age and sex stratified prevalence rates in order to calculate the number of people with a condition at the population level.

3.2.3.2. Data management

Data sets for males, females and people overall were combined into one large dataset using Microsoft Access.

3.2.4. Other UK databases

Other UK based primary care databases exist, for example not-for-profit databases, such as QRESEARCH[380] and DIN-Link[381], and commercial databases, such as THIN[382] and UK IMS disease analyser. These databases may have also provided suitable data to address the thesis objectives. However, as the largest validated and most widely used primary care database in the UK, CPRD was an appropriate choice for this series of studies.[359]

3.3. Statistical methods

3.3.1. Software

All statistical analyses were carried out using SPSS PASW Statistics (versions 18 to 20) and R.[383]

3.3.2. Incidence and prevalence rates

95% confidence intervals were calculated to provide a range of values around a prevalence or incidence rate that is believed to contain with 95% probability the true population value for the statistic. 95% Confidence intervals for incidence were calculated using the Byar approximation method. This is an adequately accurate approximation to the Poisson probabilities without the need for exact results.[384] For prevalence rates, Wilson (or score) confidence intervals were calculated.[385] This method is preferred to the asymptotic method but remains relatively easy to calculate.[385]

3.3.3. Baseline Characteristics

Mean (with the corresponding standard deviation (SD)) and median (with the corresponding interquartile range) are provided to describe the baseline characteristics depending on their distribution. In order to determine if there are statistically significant differences in the baseline characteristics between groups, baseline characteristics were compared where appropriate using the chi-squared test for categorical variables and one-way analysis of variance (ANOVA) or Kruskal–Wallis test for continuous variables (depending on the distribution of the parameter) and p-values provided. When a one-way ANOVA was carried out, Levene's test was employed to test for homogeneity of variances. If the assumption of homogeneity of variances had been violated, Welch's F was used. Both the Brown and Forsythe F-ratio and Welch's F are robust when homogeneity of variance has been broken. However, in

terms of power, Welch's F is preferred except when there is an extreme mean with a large variance.[386]

3.3.4. Survival analysis

As a means of analysing censored data, time to each endpoint was evaluated using Cox proportional hazards modelling. The Cox proportional hazards model can be conducted using SPSS and is a semi-parametric model where the distribution of the outcome and the baseline hazard are not specified.[387] Therefore, the Cox model is a popular alternative to parametric survival modelling. However, it is important to check that the proportional hazards assumption is met. The proportional hazards assumption was tested by examining the Pearson correlation between Schoenfeld residuals and the rank of survival time for cases that had progressed to death.[387] In addition, the Cox proportional hazards model can be extended to incorporate time-dependent covariates.[387] Interactions with time were used to assess the proportional hazards assumption of the extended Cox model. All covariates identified *a priori* were included in the final Cox model.

4. Incidence of type 2 diabetes in the UK between 1991 and 2010

This is the accepted version of the following article: Holden SE, Barnett AH, Peters JR, Jenkins-Jones S, Poole CD, Morgan CL, Currie CJ. The incidence of type 2 diabetes in the United Kingdom from 1991 to 2010. Diabetes Obes Metab 2013;15:844-52. doi: 10.1111/dom.12123., which has been published in final form at [http://onlinelibrary.wiley.com/doi/10.1111/dom.12123/abstract]. Deviations from the published version of this manuscript are underlined.

4.1. Introduction

4.1.1. Background

The incidence and prevalence of type 2 diabetes has been increasing in the UK.[9] Although the cause of type 2 diabetes is multi-factorial, it is largely related to obesity and physical inactivity.[8] There has been an increase in the prevalence of type 2 diabetes in children and adolescents, which is thought to be dependent on many factors such as obesity, diet, family history of diabetes, ethnicity, sedentary lifestyle, earlier onset of puberty, low birth weight and exposure to diabetes *in utero*.[388–392]

Studies in the UK secondary care population and the USA have shown that the age of diagnosis of type 2 diabetes has decreased over time.[393,394] Early onset type 2 diabetes will result in afflicted people living a larger proportion of their lives exposed to the toxicity of dysglycaemia, such that their complications could conceivably more reflect those of people with type 1 diabetes; for example, increased rates of microvascular

complications. The onset of type 2 diabetes prior to the age of 45 is an independent risk factor in the development of retinopathy after matching on diabetes duration and adjusting for traditional risk factors such as glycaemic control and hypertension.[395] In addition, youth onset type 2 diabetes in Pima Indians aged less than 20 years at diagnosis was associated with an increased incidence of end stage renal disease and mortality in middle age compared with older onset diabetes.[396] In terms of cardiovascular risk, early onset type 2 diabetes may constitute a more aggressive disease where, compared with non-diabetic controls, early onset type 2 diabetes (<45 years at diagnosis) has been associated with twice the risk of macrovascular complications when compared to usual onset type 2 diabetes (HR 7.9 versus 3.8).[397]

4.1.2. Aims and objectives

This study aimed to characterise the incidence of diabetes over the past 20 years in the UK population. We also aimed to determine if there has been an increase in the proportion of people diagnosed with diabetes who were young.

4.2. Methods

4.2.1. CPRD

Patients with type 2 diabetes were identified in the CPRD. CPRD contains clinically rich data that are collected in a non-interventional way from the daily record-keeping of primary care physicians in the UK. These pseudonymised data include patient demographics and medical history, including diagnoses, test results and prescriptions.

The data extract used for this study comprised records up to June 2011 and contained 143 million patient years of computerised data of acceptable quality for research purposes. CPRD checks the data to ensure it is of an acceptable standard and over 550 peer reviewed studies using CPRD have been published.[1] Ethical approval for this study was granted by the CPRD ISAC on 23/02/2012, protocol number 12_019R.

4.2.2. Selection Criteria

Included patients had to be newly diagnosed with type 2 diabetes between 1991 and 2010, inclusively. Patients were attributed a diagnosis of type 2 diabetes if they met one of the following criteria:

1. A diagnosis of type 2 diabetes and a prescription for a glucose lowering medicine excluding insulin

2. Diagnoses for type 1 or type 2 diabetes or diabetes where type not specified and prescriptions for more than one type of glucose-lowering medicine excluding insulin

3. A diagnosis of type 2 diabetes, no diagnosis of type 1 diabetes, no prescription for exogenous insulin or a glucose-lowering medicine other than insulin

4. A diagnosis of type 2 diabetes, no diagnosis of type 1 diabetes, a prescription for a glucose-lowering medicine but no prescription for insulin

5. A prescription for glucose biosensor strips and a medication(s) used for diabetes but no diagnosis of diabetes and no prescription for insulin

6. A diagnosis for type 2 diabetes, a diagnosis of type 1 diabetes but no prescription for insulin

7. A diagnosis of diabetes (type not specified) but no prescription for insulin.

Criteria 1, 3 and 4 include no conflicting diagnoses. Criteria 2 uses conflicting diagnoses but is based on the assumption that the use of at least two different OHAs confirms the type 2 diagnosis. Criteria 5, 6 and 7 are included as patients not treated with insulin cannot have type 1 diabetes.

4.2.3. Incidence of type 2 diabetes

The incident date of diabetes was taken as the earlier of either the date of diagnosis of diabetes or the date of the first diabetes-related prescription (glucose biosensor strip, OHA or insulin). Cases also had a minimum 'wash-in' period of one year between the incident date and the later of the patient registration date and practice up-to-standard date.

Patient data were categorised into five-year intervals by year of diagnosis and age at diagnosis. The percentage of all newly diagnosed patients in each age group was calculated by dividing the number of patients diagnosed in each age group per five-year calendar period by the total number of patients diagnosed in the same relevant five-year calendar period. The percentage of patients ≤40 years at diagnosis was

calculated in a similar way. Incidence rates were calculated yearly and by age group and five-year calendar period by dividing the number of incident cases by the number of person-years of the at risk population (without diabetes) in CPRD for the same calendar year and age group where applicable. Patients were included in the person-years estimate (denominator) from one year following the later of the up-to-standard date or the practice date until the earliest of their death date, date transferred out of practice or incident date of diabetes (patients need not necessarily have had contact with their general practice to be included). Incidence was compared within age groups over time by calculating an age-and-sex-stratified standardised incidence ratio (SIR), akin to a standardised mortality rate (SMR).

4.2.4. Statistical analysis

Statistical analyses were carried out using SPSS-18 and R.[383] Changes in SIRs were compared by means of the Byar approximation Poisson method.[398] Baseline characteristics were compared between five-year calendar periods using Mantel-Haenszel linear-by-linear chi-squared test for categorical variables and one-way ANOVA or Kruskal-Wallis test for continuous variables, depending on their distribution. Levene's test was employed to test for homogeneity of variances. If the assumption of homogeneity of variances had been violated and group sizes were unequal, Welch's F was used. Differences between five-year calendar periods were explored using Games-Howell procedure, which can be used when population variances and sample sizes differ. Kendall's tau-b was used to determine if there was a significant association between percentage diagnosed and five-year calendar period. Confidence intervals for incidence rates were calculated using the Byar approximation method and for

proportions using mid-P confidence interval adaptation of the Clopper-Pearson interval.

4.3. Results

4.3.1. Baseline Characteristics

Baseline characteristics by year and age group at diagnosis are detailed in (Table 4.1). In each five-year calendar period, slightly more newly diagnosed patients were female and more patients>40 were male. For people aged ≤40 at diagnosis, BMI changed from a mean (SD) of 32.2 kg/m2 (7.7 kg/m2) in 1991–1995 to 31.6 kg/m2 (7.6 kg/m2) in 1996–2000 (p=0.649), 32.6 kg/m2 (7.7 kg/m2) in 2001–2005 (p=0.003) and 30.8 kg/m2 (8.0kg/m2) in 2006–2010 (p<0.001). For people >40 at diagnosis, mean BMI increased with each successive five-year calendar period from a mean of 29.2 kg/m2 (5.3 kg/m2) in 1991–1995 to 30.8 kg/m2 (6.1 kg/m2) in 2006–2010 (p<0.001).

For patients aged ≤40 years at diagnosis, mean (SD) HbA_{1c} at baseline was 8.3% (3.0%) in 1991–1995, decreasing to 6.1% (2.2%) in 1996–2000 (p<0.001) before increasing to 6.7% (2.5%) in 2001–2005 (p<0.001) and 7.4% (2.6%) in 2006–2010 (p<0.001). For patients aged >40 years at diagnosis HbA_{1c} was 9.0% (2.9%) in 1991–1995, decreasing to 7.6% (2.6%) in 1996–2000 (p<0.001), 7.5% (2.3%) in 2001–2005 (p<0.001) and 7.5% (2.2%) in 2006–2010 (p=0.776). Mean systolic and diastolic blood pressure and total cholesterol levels decreased in each five-year calendar period between 1991 and 2010 for patients aged >40 at diagnosis. For patients ≤40 at diagnosis, systolic and diastolic blood pressure and total cholesterol were lower in 2006–2010 than any other year. The number of GP contacts—an indicator of general morbidity—in the year prior to diagnosis of type 2 diabetes increased during the study period from a median (interquartile range, IQR) of 5.0 (2.0–9.0) and 6.0 (3.0–11.0) contacts in 1991–1995 to 7.0 (3.0–12.0, p<0.001) and 8.0 (4.0–15.0, p<0.001) contacts in 2006–2010 for patients aged ≤40 and >40 at diagnosis, respectively. The time to first drug treatment for type 2

diabetes following diagnosis decreased from a median (IQR) of 0.4 (0.0–3.2) and 0.5 (0.0–3.1) years in 1991–1995 to 0.0 (0.0–0.3, p<0.001) and 0.1 (0.0–0.6, p<0.001) years in 2006–2010 for patients aged ≤40 and >40 at diagnosis, respectively. There was no change in the median score for the adjusted Charlson morbidity index during the study period for patients aged ≤40 years at diagnosis and decreased from 4.0 (3.0–5.0) in 1991–1995 to 3.0 (2.0–5.0) in 1996–2000, 2001–2005 and 2006–2010 for patients aged >40 at diagnosis. More patients had suffered from conditions that could be associated with a complication of diabetes prior to their diagnosis of type 2 diabetes in increasing five–year calendar periods and there was a significant difference between groups for coronary heart disease (p<0.001), cerebrovascular disease (p<0.001), diabetic foot and peripheral vascular disease (p<0.001), eye-related complications (p<0.001) and end stage renal disease (p<0.001) for patients aged >40 at diagnosis.

4.3.2. Standardized incidence ratio

The SIR increased within each five-year calendar period from 1991–1995 (SIR=100) to 158 (CI 157–160, p<0.001), 237 (235–238, p<0.001) and 275 (273–276, p<0.001), respectively (Table 4.2). For those aged 40 years and under, the respective SIRs were 217 (209–226, p<0.001), 327 (320–335, p<0.001) and 598 (589–608, p<0.001).

Table 4.1 Baseline characteristics for patients diagnosed with type 2 diabetes before and after 40 years of age

Parameter	1991–1995		1996–2000		2001–2005		2006–2010		p-value	
	≤40	>40	≤40	>40	≤40	>40	≤40	>40	≤40	>40
N	642	10,241	2,752	29,846	7,519	81,324	15,326	108,621		
Males, n (%)	312 (49%)	5,404 (53%)	1,233 (45%)	15,613 (52%)	3,397 (45%)	42,452 (52%)	6,546 (43%)	56,925 (52%)	<0.001	0.987
Age (years), mean (SD)	32.5 (7.4)	66.0 (11.8)	30.9 (8.6)	65.3 (12.1)	31.1 (8.5)	65.1 (12.1)	29.4 (9.4)	64.2 (12.6)	<0.001	<0.001
Smoking status, n (%)	438 (68%)	7,016 (69%)	2,094 (76%)	25,329 (85%)	6,154 (82%)	74,601 (92%)	13,477 (88%)	106,938 (98%)	0.159	<0.001
Non-smoker, n (%)	266 (61%)	4,320 (62%)	1,185 (57%)	13,835 (55%)	3,195 (52%)	33,704 (45%)	7,069 (52%)	44,701 (42%)		
Ex-smoker, n (%)	49 (11%)	1,174 (17%)	206 (10%)	5,859 (23%)	889 (14%)	25,664 (34%)	2,639 (20%)	43,431 (41%)		
Current smoker, n (%)	123 (28%)	1,522 (22%)	703 (34%)	5,635 (22%)	2,070 (34%)	15,233 (20%)	3,769 (28%)	18,806 (18%)		
HbA_{1c}, %										
n (%)	57 (9%)	973 (10%)	1,327 (48%)	10,941 (37%)	3,879 (52%)	41,732 (51%)	4,372 (29%)	51,103 (47%)		
mean (SD)	8.3 (3.0)	9.0 (2.9)	6.1 (2.2)	7.6 (2.6)	6.7 (2.5)	7.5 (2.3)	7.4 (2.6)	7.5 (2.2)	<0.001	<0.001
BMI (kg/m^2)										
n (%)	244 (38%)	4,367 (43%)	888 (32%)	12,836 (43%)	3,275 (44%)	46,774 (58%)	7,103 (46%)	70,298 (65%)		
Mean (SD)	32.2 (7.7)	29.2 (5.3)	31.6 (7.6)	29.9 (5.7)	32.6 (7.7)	30.5 (5.8)	30.8 (8.0)	30.8 (6.1)	<0.001	<0.001
Weight: males (kg)										
n (%)	128 (41%)	2,511 (46%)	437 (35%)	7,265 (47%)	1,559 (46%)	25,624 (60%)	3,080 (47%)	38,687 (68%)		
mean (SD)	95.8 (22.5)	86.5 (15.8)	97.5 (25.6)	89.5 (17.1)	100.1 (26.7)	91.7 (17.7)	96.3 (28.3)	93.6 (18.9)	<0.001	<0.001

Parameter	1991–1995		1996–2000		2001–2005		2006–2010		p-value	
	≤40	>40	≤40	>40	≤40	>40	≤40	>40	≤40	>40
Weight: females (kg)										
n (%)	120 (36%)	2,040 (42%)	505 (33%)	6,021 (42%)	1,839 (45%)	21,914 (56%)	4,312 (49%)	32,269 (62%)		
mean (SD)	86.3 (22.3)	76.1 (16.3)	83.2 (22.8)	77.7 (17.5)	87.4 (23.8)	79.2 (17.8)	80.3 (24.6)	79.7 (18.8)	<0.001	<0.001
Time to 1st treatment (years):									<0.001	<0.001
mean (SD)	2.2 (3.4)	2.0 (3.0)	1.7 (2.5)	1.7 (2.4)	1.0 (1.7)	1.4 (2.0)	0.3 (0.7)	0.5 (0.9)		
median (IQR)	0.4 (0.0–3.2)	0.5 (0.0–3.1)	0.4 (0.0–2.4)	0.5 (0.0–2.6)	0.1 (0.0–1.2)	0.4 (0.0–2.3)	0.0 (0.0–0.3)	0.1 (0.0–0.6)		
BP										
n (%)	309 (48%)	6,241 (61%)	1,335 (49%)	19,765 (66%)	4,543 (60%)	68,199 (84%)	8,962 (58%)	93,307 (86%)		
Diastolic BP, mean (SD)	82.7 (11.1)	85.3 (10.9)	80.7 (12.3)	84.4 (10.7)	81.5 (12.1)	82.5 (11.0)	78.6 (11.8)	80.1 (10.8)	<0.001	<0.001
Systolic BP, mean (SD)	132 (19)	150 (21)	128 (19)	148 (20)	130 (18)	144 (19)	125 (17)	138 (18)	<0.001	<0.001
Number of GP contacts:									<0.001	<0.001
mean (SD)	7.0 (6.5)	8.0 (7.3)	7.2 (7.4)	9.0 (8.3	7.3 (7.8)	9.1 (9.0)	9.1 (9.6)	10.9 (11.0)		
median (IQR)	5 (2–9)	6 (3–11)	5 (2–10)	7 (3–12)	5 (2–10)	7 (3–12)	7 (3–12)	8 (4–15)		
Total cholesterol (mmol/l)									<0.001	<0.001
n (%)	69 (11%)	1,250 (12%)	556 (20%)	9,581 (32%)	2,832 (38%)	54,182 (67%)	5,086 (33%)	82,459 (76%)		
mean (SD)	6.0 (1.3)	6.2 (1.2)	5.5 (1.2)	5.8 (1.2)	5.4 (1.2)	5.5 (1.2)	5.3 (1.2)	5.1 (1.2)		
Charlson Index:									<0.001	<0.001
mean (SD)	1.2 (0.8)	1.7 (1.2)	0.8 (0.8)	1.5 (1.3)	0.8 (0.9)	1.5 (1.3)	1.1 (0.8)	1.8 (1.5)		

Parameter	1991–1995		1996–2000		2001–2005		2006–2010		p-value	
	≤40	>40	≤40	>40	≤40	>40	≤40	>40	≤40	>40
median (IQR)	1 (1–1)	1 (1–2)	1 (0–1)	1 (1–2)	1 (0–1)	1 (1–2)	1 (1–1)	1 (1–3)		
Adjusted Charlson Index:									<0.001	<0.001
mean (SD)	1.2 (0.8)	3.8 (2.0)	0.8 (0.8)	3.3 (2.2)	0.8 (0.9)	3.3 (2.3)	1.1 (0.8)	3.6 (2.5)		
median (IQR)	1 (1–1)	4 (3–5)	1 (0–1)	3 (2–5)	1 (0–1)	3 (2–5)	1 (1–1)	3 (2–5)		
Diabetic complications:										
CHD (%)	0 (0%)	0 (0.0%)	9 (0%)	1,011 (3%)	49 (1%)	5,738 (7%)	83 (1%)	9,626 (9%)	0.147	<0.001
CVD (%)	0 (0%)	0 (0.0%)	1 (0%)	324 (1%)	14 (0%)	1,638 (2%)	42 (0%)	2,884 (3%)	0.005	<0.001
Foot and PVD (%)	0 (0%)	0 (0.0%)	1 (0%)	138 (0%)	3 (0%)	638 (1%)	7 (0%)	956 (1%)	0.622	<0.001
Eye (%)	0 (0%)	0 (0.0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0.849	<0.001
ESRD (%)	0 (0%)	0 (0.0%)	3 (0%)	109 (0%)	33 (0%)	657 (1%)	134 (1%)	1,756 (2%)	<0.001	<0.001

CHD = coronary heart disease, CVD = cerebrovascular disease, PVD = peripheral vascular disease, ESRD = end stage renal disease. Smoking status was the nearest status recorded prior to the index date. For BMI, HbA_{1c}, weight, blood pressure (BP), total cholesterol the nearest record to the index date was taken, provided it was no more than 365 days prior to or 30 days after the index date. The number of GP contacts represents the number of GP contacts in the year prior to the index date. Diabetic complications refer to whether patient had record of a diabetic complication prior to index date.

Table 4.2 Standardized incidence ratio (SIR: 1991–1995=100) for five-yearly periods to 2010.

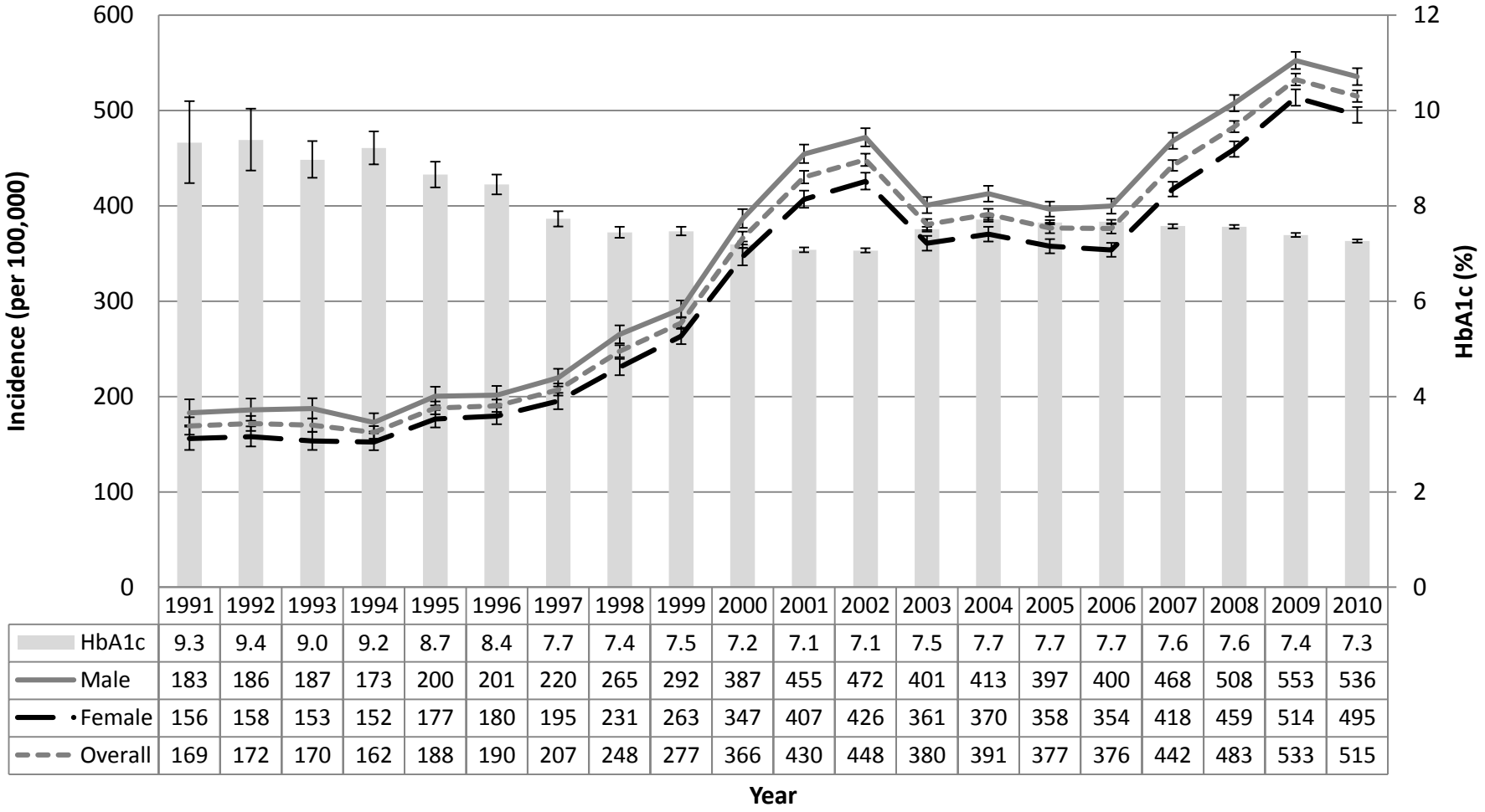
Year group	Observed	Expected	SIR	95% CI		p
All subjects						
1991–1995	10,883	n/a	100			
1996–2000	32,596	20,601	158	157	160	<0.001
2001–2005	88,835	37,545	237	235	238	<0.001
2006–2010	123,932	45,135	275	273	276	<0.001
Males						
1991–1995	5,716	n/a	100			
1996–2000	16,846	10,945	154	152	156	<0.001
2001–2005	45,849	20,209	227	225	229	<0.001
2006–2010	63,471	24,499	259	257	261	<0.001
Females						
1991–1995	5,167	n/a	100			
1996–2000	15,750	9,656	163	161	166	<0.001
2001–2005	42,986	17,336	248	246	250	<0.001
2006–2010	60,461	20,636	293	291	295	<0.001
Under 40 years						
1991–1995	577	n/a	100			
1996–2000	2,496	1,148	217	209	226	<0.001
2001–2005	6,798	2,077	327	320	335	<0.001
2006–2010	14,073	2,352	598	589	608	<0.001

4.3.3. Specific incidence rates

The estimated incidence of clinically diagnosed and recorded type 2 diabetes increased between 1991 and 2002 from 169 newly diagnosed people per 100,000 person-years (95% CI 160–178) to 448 (95% CI 442–455) before decreasing to 376 (95% CI 371–382) per 100,000 in 2006 (Figure 4.1). By 2009, the incidence of type 2 diabetes had increased to 533 (95% CI 526–539) per 100,000 before decreasing slightly to 515 (95% CI 509–521) per 100,000 in 2010. The incidence of type 2 diabetes for males and females followed a similar pattern, but incidence was higher for males than for females. HbA_{1c} levels at baseline were 9.3% (95% CI 8.5%–10.2%), 7.1% (95% CI 7.0%–7.1%), 7.7% (95% CI 7.6%–7.7%), 7.4% (95% CI 7.4%–7.4%) and 7.3% (95% CI 7.2%–7.3%) in 1991, 2002, 2006, 2009 and 2010, respectively.

The incidence rate for diagnosed and recorded type 2 diabetes increased with each increasing five-year calendar period for all age groups and for both genders, with the exception of females who were 90 years and over, where the incidence rate fell from 482 to 452 people per 100,000 in the final two five-year calendar periods (Figure 4.2a and Figure 4.2b). Overall, between 1996 and 2005, the incidence rate was highest in the 70–74 age group at 892 and 1,415 people per 100,000 for 1996–2000 and 2001–2005, respectively. For 1991–1995, the incidence rate was highest in the 75–79 age group at 605 people per 100,000. In 2006–2010, the highest incidence rates were seen in the 70–74 and 75–79 age groups at 1,486 per 100,000. After the age of 40 years, the incidence was higher in males for each five-year calendar period (Figure 4.2a and Figure 4.2b). However, females had a higher incidence than did males for many of the age groups below 40 years, including the age groups between 20 and 34 years for all five-year calendar periods.

Figure 4.1 Incidence of diagnosed and recorded type 2 diabetes per 100,000 population by year

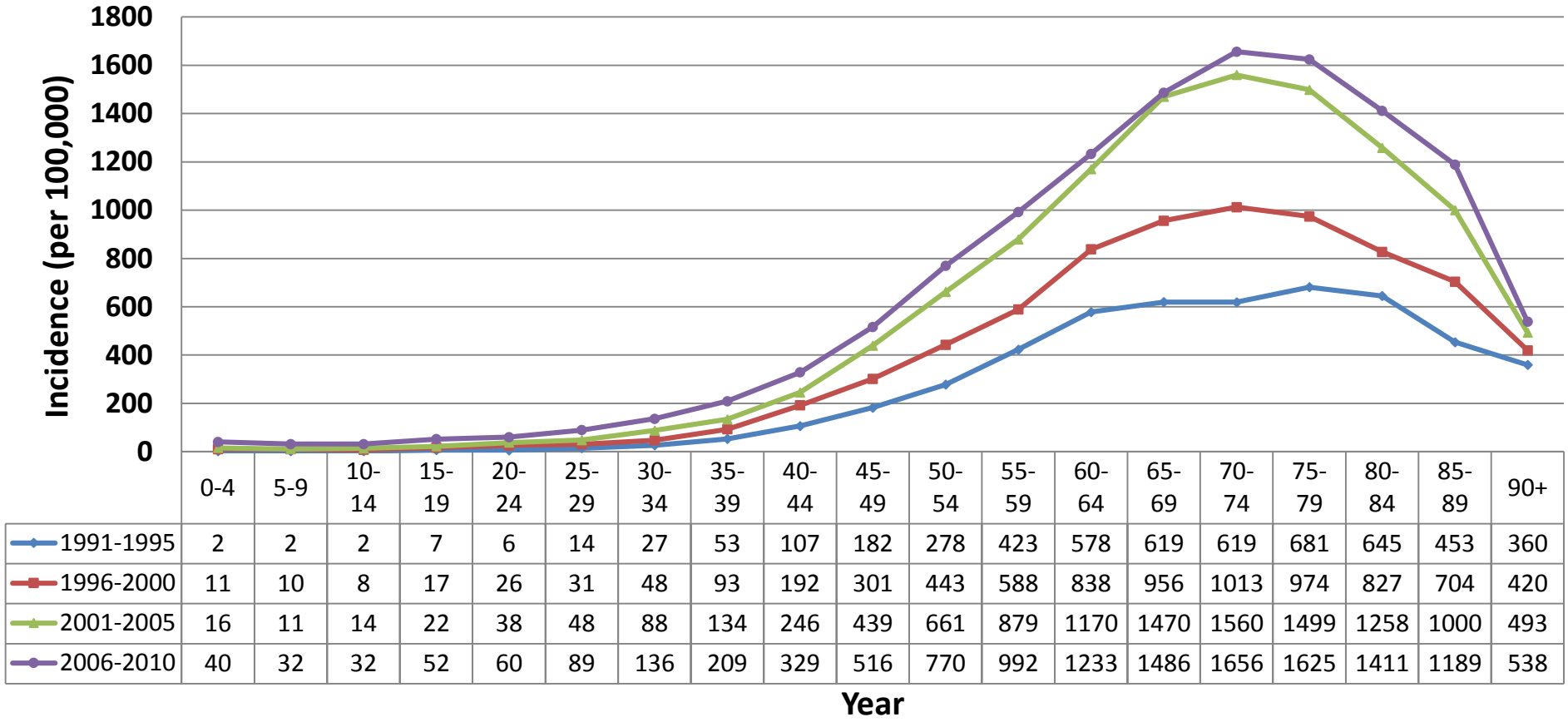


	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
HbA1c	9.3	9.4	9.0	9.2	8.7	8.4	7.7	7.4	7.5	7.2	7.1	7.1	7.5	7.7	7.7	7.7	7.6	7.6	7.4	7.3
Male	183	186	187	173	200	201	220	265	292	387	455	472	401	413	397	400	468	508	553	536
Female	156	158	153	152	177	180	195	231	263	347	407	426	361	370	358	354	418	459	514	495
Overall	169	172	170	162	188	190	207	248	277	366	430	448	380	391	377	376	442	483	533	515

Year

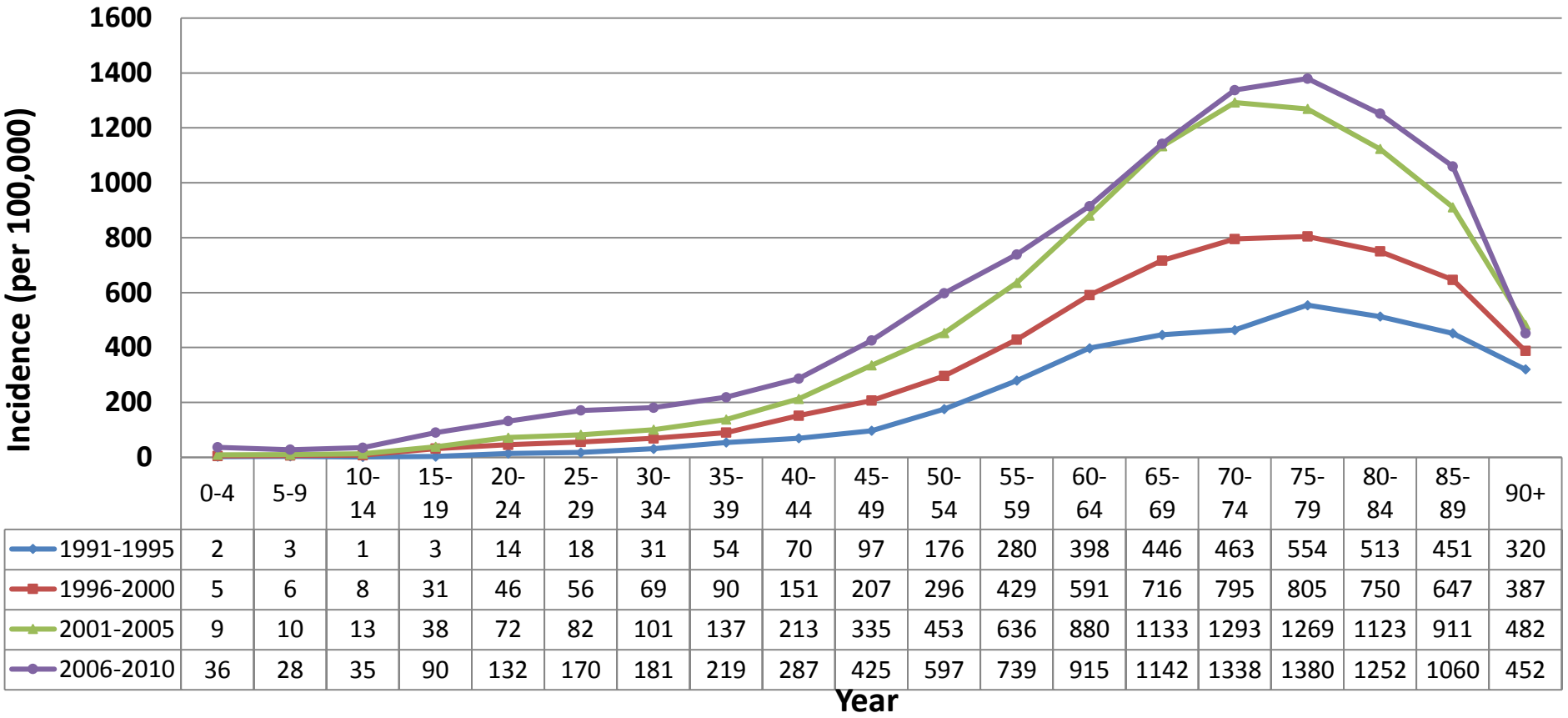
Figure 4.2 Age-specific incidence of new cases of type 2 diabetes per 100,000 population by year

a) Males



	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90+
1991-1995	2	2	2	7	6	14	27	53	107	182	278	423	578	619	619	681	645	453	360
1996-2000	11	10	8	17	26	31	48	93	192	301	443	588	838	956	1013	974	827	704	420
2001-2005	16	11	14	22	38	48	88	134	246	439	661	879	1170	1470	1560	1499	1258	1000	493
2006-2010	40	32	32	52	60	89	136	209	329	516	770	992	1233	1486	1656	1625	1411	1189	538

b) Females



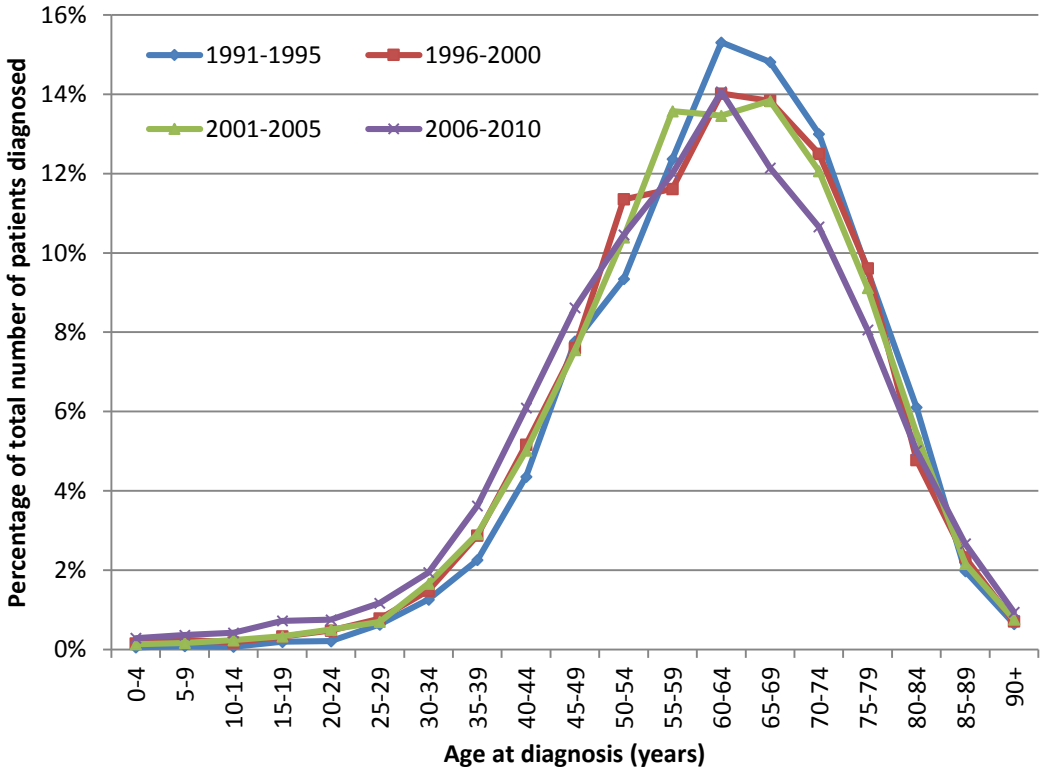
	0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	85-89	90+
1991-1995	2	3	1	3	14	18	31	54	70	97	176	280	398	446	463	554	513	451	320
1996-2000	5	6	8	31	46	56	69	90	151	207	296	429	591	716	795	805	750	647	387
2001-2005	9	10	13	38	72	82	101	137	213	335	453	636	880	1133	1293	1269	1123	911	482
2006-2010	36	28	35	90	132	170	181	219	287	425	597	739	915	1142	1338	1380	1252	1060	452

A larger percentage of patients were diagnosed between 65 and 69 years of age between 1991 and 2005 than any other age group. However, between 2006 and 2010, the most common age at diagnosis was lower, at 60–64 years. For males, the largest percentage of patients was diagnosed between 65 and 69 years of age from 2001–2005, but between 60 and 64 years of age for 1991–1995, 1996–2000 and 2006–2010 (Figure 4.3a). The largest percentage of females was diagnosed between the ages of 70 to 74 years for 1991–2005 (Figure 4.3c). This had decreased to 60–64 years of age between 2006 and 2010.

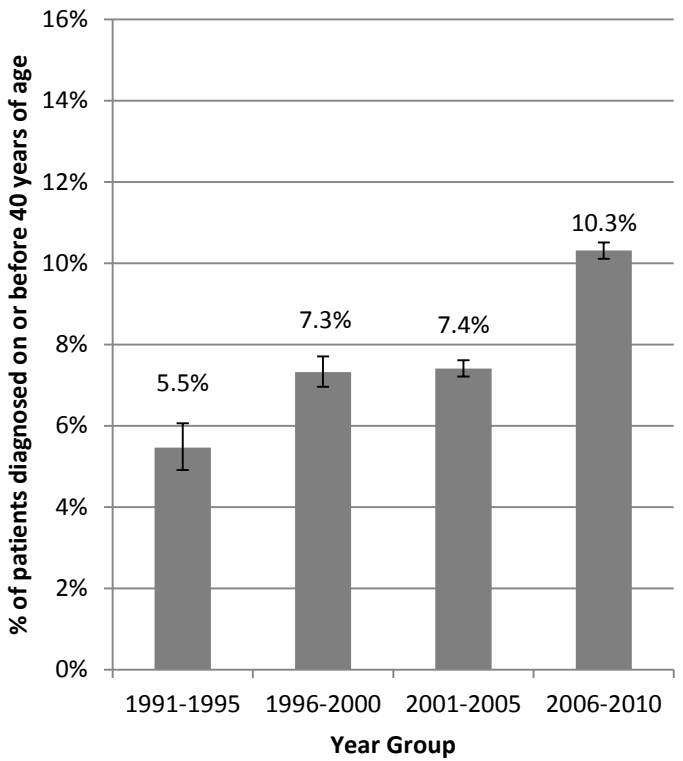
The percentage of patients aged 40 years or less at diabetes diagnosis increased with each increasing five-year calendar period for males (Figure 4.3b) and increased between 1991–1995 and 2006–2010 in females (Figure 4.3d). However, there was no increase observed between 1996–2000 and 2001–2005. Overall, the percentage of patients diagnosed on or before the age of 40 years was 5.9% (95% CI 5.5%–6.3%), 8.4% (95% CI 8.2%–8.7%), 8.5% (95% CI 8.3%–8.6%)and 12.4% (95% CI 12.2%–12.5%) for 1991–1995, 1996–2000, 2001–2005 and 2006–2010, respectively. There was a significant association between five-year calendar period and the number of patients diagnosed before and after the age of 40 ($p<0.001$). However, there were differences between the incidence in males and females, where the incidence was higher in females at earlier ages.

Figure 4.3 Percentage of new cases of type 2 diabetes between 1991 and 2010 by age group and calendar period

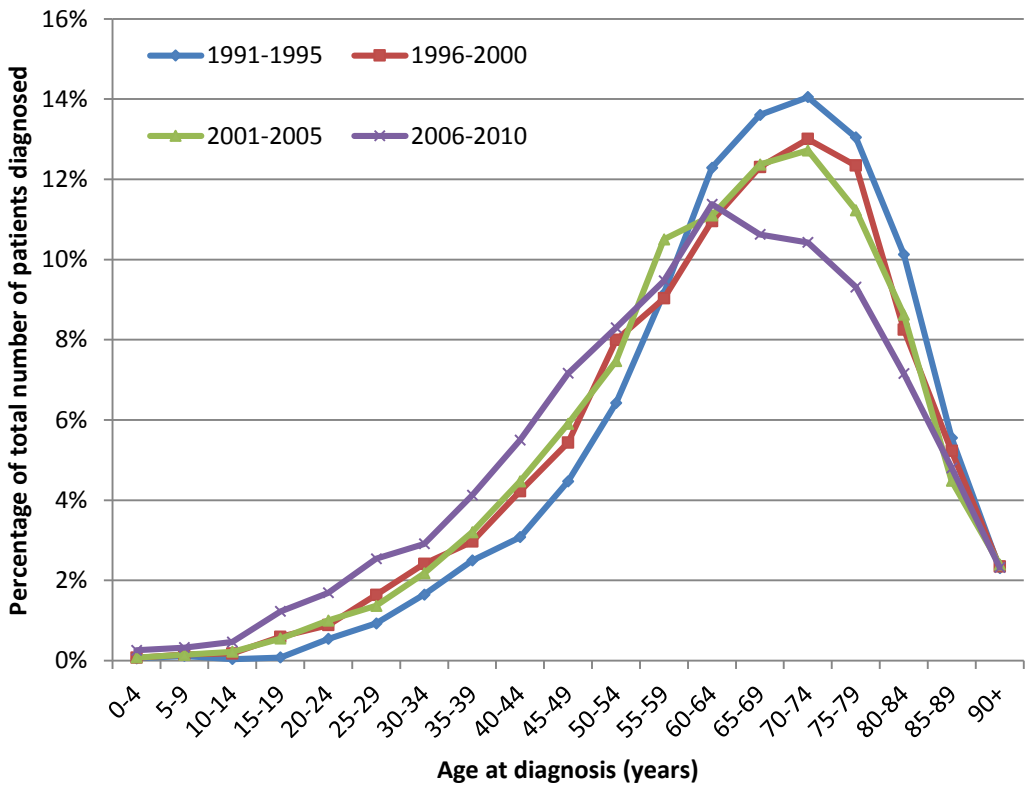
a) Males, all ages



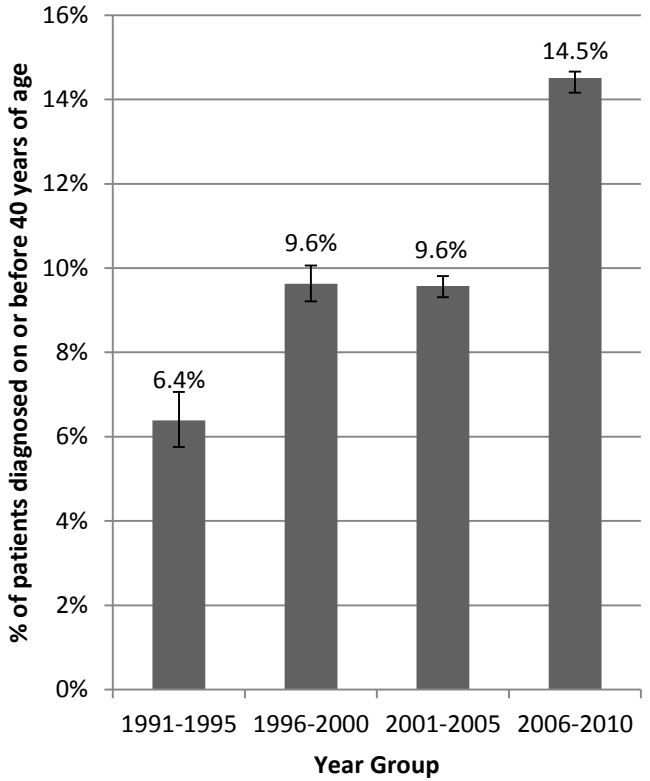
b) Males diagnosed at or before 40 years of age



Females, all ages



a) Females diagnosed at or before 40 years of age



4.4. Discussion

4.4.1. Main findings

The incidence of clinically diagnosed and recorded type 2 diabetes increased markedly between 1991 and 2010 in most age groups. Furthermore, the incidence rate increased with increasing age until 75 years of age. Importantly, not only was the overall incidence increasing, the proportion of people who were aged 40 years or less at diagnosis doubled.

The study results could reflect an increase in the incidence of type 2 diabetes in the UK population and a decrease in the age of onset. However, other factors may also have contributed to this increase including earlier detection of type 2 diabetes in at risk groups, improved recording of type 2 diabetes in CPRD and implementation of new criteria for the diagnosis of type 2 diabetes. These factors are discussed in more detail below in Chapter 4.4.2.

4.4.2. Comparison with existing literature

The incidence results are supported by incidence and prevalence rates previously demonstrated for the UK,[9] USA[399] and worldwide.[400] Conversely, between 2004 and 2006, the incidence of diabetes in Denmark has decreased slightly.[156] The primary modifiable risk factor contributing to development of type 2 diabetes is energy balance as measured by BMI as a proxy for obesity. In the general UK population, both the prevalence and severity of obesity has been rising since 1993.[63] Between 1993 and 2010, the proportion of the UK population who were estimated to be obese increased from 13% to 26% for men and 16% to 26% for women.[63] For children, the prevalence

of obesity has increased between 1995 and 2010 from 11% to 17% and from 12% to 15% for boys and girls, respectively.[63] However, the percentage of adults meeting recommended levels for physical activity increased in the UK from 32% and 21% in 1997 to 42% and 31% in 2008 for men and women, respectively.[63] There is an inverse relationship between BMI and age of onset of type 2 diabetes[22] and intensive lifestyle intervention with a minimum of 7% weight loss and 150 minutes of physical activity per week reduced the incidence rate for diabetes by 58%.[23] A study based in Germany revealed that severe weight gain between the ages of 25 and 40 was associated with a higher risk of diabetes than if weight was stable in early adulthood and increased in later life (1.5 and 4.3 times the risk for males and females, respectively) and the age at diagnosis was also lowered (five and three years for males and females, respectively).[401] For the study period, there was an increase in mean BMI at baseline for people diagnosed after the age of 40 for each successive five-year calendar period and both male and female weight increased in each five-year group during the study period. However, for people aged 40 years or less at diagnosis, the mean BMI fluctuated between five-year calendar periods. A similar pattern was also observed for mean weight for both males and females in this age group. The decrease in 2006–2010 could be partly accounted for by the increased percentage of children and adolescents diagnosed in this five-year calendar period.

The increase in the incidence of type 2 diabetes and the proportion of patients aged 40 years or less at diagnosis may be due, at least in part, to enhanced detection of type 2 diabetes. Unlike type 1 diabetes, the symptoms of type 2 diabetes are not always obvious and the condition can remain undiagnosed for many years. A study carried out between 1978 and 1982 found that the actual onset of type 2 diabetes may be at least four to seven years before clinical diagnosis.[17] Therefore, enhanced detection of type 2

diabetes may have an impact on how soon diagnosis is achieved after onset of the condition. Although systematic population screening for type 2 diabetes is not recommended in the UK, early detection of type 2 diabetes in high risk groups is likely to have contributed to the increased incidence rate observed over the study period.[402] In the last decade, changes to the GMS and Pharmacy Contracts, the implementation of the National Diabetes Framework, and local initiatives have increased the awareness of diabetes.[403,404] For example, the QOF was introduced on 1st April 2004.[404] In addition, changes have been made to the criteria for diagnosing type 2 diabetes during the study period. In 2000, the WHO new diagnostic criteria for the diagnosis of diabetes were implemented in the UK, which included lowering the threshold for diagnosing diabetes by FPG from 7.8 mmol/l to 7.0 mmol/l.[405] These changes would have led to an increase in the number of patients diagnosed with type 2 diabetes and a decrease in the age at diagnosis. If the increase in incidence is a result of enhanced detection, this could be viewed positively as patients will receive appropriate diabetes care at an earlier stage of their disease. In support of this theory of an ascertainment effect, HbA_{1c} levels at baseline followed an inverse pattern when compared with annual incidence rates for type 2 diabetes. However, it is important to note that there were a large amount of missing data in the earlier years of the study period. Blood pressure and total cholesterol decreased throughout the study period, which may be an indication of improved detection of type 2 diabetes in patients who are already being treated for hypercholesterolaemia and hypertension. The increased use of statins is likely to account for the reduction in baseline cholesterol seen during the study period. In a meta-analysis conducted by Rajpathak and colleagues, statin use was associated with a small increased risk of diabetes (RR 1.13, 95% CI 1.03–1.23) when hypothesis-testing RCTs were combined. However, this increase in risk was no longer

significant following the addition of data from West of Scotland Coronary Prevention Study (WOSCOPS), a hypothesis-generating RCT (1.06, 95% CI 0.93–1.25).[406] However, when used for primary and secondary prevention of cardiovascular disease, statins have been show to significantly reduce the risk of cardiovascular events and death.[407–410] During the study period, more diabetic complications have been recorded in relation to increasing five-year calendar periods. This could indicate a number of factors; for example, improved survival of patients with advanced disease, or patients suffering from more advanced disease at diagnosis. Improved recording of diagnoses in CPRD could also account for this trend. There was a sharp increase in the annual incidence between 1999 and 2002, followed by a decline and a plateau between 2003 and 2006. One possible explanation could be that enhanced detection of type 2 diabetes between 1999 and 2002 could have led to the removal of patients from the undiagnosed population that would have otherwise presented later in the course of their disease i.e. during the period 2003 to 2006. The proportion of people diagnosed prior to the age of 40 was higher for females compared with males and this percentage increased with increasing 5-year calendar period. This is likely to be due to an increased focus on gestational diabetes as a marker for the later development of type 2 diabetes leading to improved detection and an earlier diagnosis.

Irrespective of the cause, the results of this study show that type 2 diabetes is common under the age of 40 years. Earlier onset type 2 diabetes (aged <40 years at recorded diagnosis) could result in longer disease duration and lead to an increased risk of developing diabetic complications. This is likely to place an increasing burden on healthcare resources, and increased patient morbidity may lead to a poorer quality of life. An earlier age of onset of type 2 diabetes may also lead to mortality occurring at a younger age. The Framingham Heart Study showed that the risk of CHD and CHD-

related death increased with increasing duration of diabetes.[411] However, the current definition of diabetes is different to the definition used in the Framingham Heart Study. The Northern Manhattan Study found that diabetes duration was independently associated with an increased risk of ischaemic stroke.[412] In addition, youth onset type 2 diabetes has been linked to an increased risk of developing diabetic complications including cardiovascular disease and retinopathy.[393,397,413] The Vascular Risk Assessment and Management Programme called NHS Health Check has been gradually introduced in England for everyone aged 40 to 74.[414] However, it is important to consider if screening programmes should include patients under the age of 40 as earlier diagnosis will lead to the earlier initiation of appropriate diabetes care and treatment. Conversely, the results from the Anglo-Danish-Dutch Study of Intensive Treatment In People with Screen Detected Diabetes in Primary Care (ADDITION)-Cambridge trial demonstrated that an invitation to one round of screening for type 2 diabetes in people aged 40–69 at high risk of having prevalent undiagnosed diabetes was not associated with a reduction in all-cause, cardiovascular-related or diabetes-related mortality where median duration of follow-up was 9.6 years.[415]

A study based on the population of Cardiff and the Vale of Glamorgan found that diabetes prevalence increased from 2.5% to 3.9% between 1996 and 2005 and during the same period the percentage of patients with diagnosed diabetes with recorded complications relating to diabetes decreased.[416] It was hypothesised that the increase in prevalence was largely due to an ascertainment effect.[416] Therefore, as the incidence of diagnosed type 2 diabetes increases, a similarly large increase in diabetes complications may not necessarily follow if patients are diagnosed earlier in the course of their disease.[416]

Medical conditions like type 2 diabetes may be better recorded in CPRD in more recent years and this could have contributed to the increase in incidence rate over time. The introduction of QOF incentivised GPs to keep accurate records of patients with diabetes.[404] However, the diabetes presentation date was taken as the earlier of the first diagnoses for diabetes or the first prescription for a glucose-lowering therapy.

4.4.3. Strengths and weaknesses of the study

As already discussed, the main limitation of this study is the use of age of diagnosis to understand any trends in the age of onset of type 2 diabetes. In addition, the recording of measurements such as weight, BMI, total cholesterol, smoking status and BP improved during the study period. For BMI, the percentage of patients with a recorded BMI increased from 38% in 1991–1995 to 46% in 2006–2010 for those patients aged 40 years or less at diagnosis and this may be skewed as overweight patients are more likely to have their weight measured. In addition, a consensus statement recommending the use of a Diabetes Control and Complications Trial (DCCT)-aligned HbA_{1c} method in the UK was not published until 2000 and HbA_{1c} levels in the early period may not have been standardised throughout the UK.[417] Therefore, comparisons of mean HbA_{1c} levels between five-year calendar periods should be interpreted with caution. One other study limitation concerns the allocation of a diagnosis of type 2 diabetes to patients in CPRD: in particular, the coding of diabetes may have changed in recent years. The term IDDM was used more commonly in earlier years, whereas 'type 1 diabetes' is now more frequently used. Some people with type 2 diabetes and receiving prescriptions for insulin may have been attributed a code for IDDM, leading to diabetes type being misclassified; this may exaggerate any increase in incidence

seen during the study period. In addition, the criteria used in this study to attribute a diagnosis of type 2 diabetes to CPRD patients did not utilise BMI or laboratory data, which might have improved the classification of diabetes type.[418] Age was not used to classify diabetes type in this study as we were specifically investigating the proportion of people with type 2 diabetes in younger age groups.

4.4.4. Conclusion

The incidence of clinically diagnosed and recorded type 2 diabetes has increased three-fold between 1991 and 2010. The proportion people with type 2 diabetes diagnosed with the condition before the age of 40 continued to increase as a proportion of those diagnosed and these people have a greater opportunity to develop long-term complications.

5. Prevalence, glucose control and survival of people with type 1 and type 2 diabetes in the UK from 1991 to 2013

5.1. Introduction

5.1.1. Background

In England in 2012, 26% of adults were obese (BMI ≥30kg/m^2), and approximately one in three girls and boys aged 2 to 15 years was classed as either overweight or obese.[419] Obesity is the primary risk factor driving incident type 2 diabetes. Using data from UK general practice, the prevalence of diabetes in the UK was estimated to be 2.8% in 1995, increasing to 4.3% in 2005.[9] Figures published by Diabetes UK using data from QOF reported that the number of people with diabetes in the UK increased from 1.4 million in 1996 to 2.8 million in 2010.[420] The incidence of type 2 diabetes increased markedly between 1991 and 2010 in the UK from 169 to 515 per 100,000 person-years.[421] During the same period, the percentage of people aged ≤40 years at diagnosis increased with each increasing five-year calendar period (5.9% for 1991–1995 and 12.4% for 2006–2010).[421] In addition, the prevalence of people injecting insulin also increased from 2.4 per 1000 population in 1991 to 6.7 per 1000 in 2010.[422] This trend was largely due to an increase in the prevalence of insulin users with a diagnosis of type 2 diabetes.[422] A recent study published in *JAMA* found that the prevalence of diabetes in the US doubled between 1990 and 2008 before reaching a plateau between 2008 and 2012.[423]

People with type 2 diabetes are at risk of developing microvascular and macrovascular complications, and their risk of death as people is at least twice that of people without diabetes.[40] In 2010–2011 in the UK, type 2 diabetes cost an estimated £9 billion in

direct costs and £13 billion in indirect costs and accounted for approximately 10% of all NHS resource expenditure.[41] In 2005, 11.6% of deaths in people aged 20–79 in England were attributed in some way to diabetes.[65] In people with type 1 and type 2 diabetes, life expectancy is thought to be reduced by 20 and 10 years, respectively.[424–426] Diabetes is the fifth leading cause of death in the world.[40]

5.1.2. Aims and objectives

The aim of this study was to characterise the prevalence of diabetes over the past 23 years in the UK population, and to determine whether glucose control and the risk of all-cause mortality have changed during the same period.

5.2. Methods

5.2.1. The Clinical Practice Research Datalink (CPRD)

The data source used for this study was CPRD primary care dataset (CPRD GOLD).[427] CPRD GOLD contains clinically rich, pseudonymised data collected in a non-interventional manner from the daily record-keeping of primary-care physicians in the UK. The dataset includes: patient demographic and registration information, consultations, medical history and diagnoses, test results, immunisations, referrals, outpatient letters and prescriptions. CPRD GOLD is broadly representative of the UK population and contains to date over 12 million research-quality patients registered at 660 practices. The data extract used in this study included records up to June 2012.

For a proportion of participating practices between 1997 and 2011, CPRD records have been linked to the NHS HES dataset. Details of inpatient admissions were therefore available between these dates for those patients with a linked HES record.

The CPRD ISAC approved the protocol for this study on 22nd September 2014 (reference number 14_172AR).

5.2.2. Patient selection criteria

In this retrospective study, patients denoted by CPRD as being of acceptable research quality were identified if they had type 1 or type 2 diabetes and presented with diabetes before or during the study period (1991–2013). A diagnosis of type 1 or type 2 diabetes was allocated based on a series of decision rules, which utilised the following patient information: age at diagnosis, diagnosis type (type 1, type 2 or type unspecified, recorded as Read codes in primary care data or as ICD-10 codes in HES

data), history of prescriptions for insulin and other types of glucose-lowering medications, BMI and HbA_{1c} (see Table 5.1). Only those patients with at least one recorded prescription for a glucose-lowering medication or at least one diagnosis for diabetes recorded in the CPRD GOLD clinical table or in HES were included in the study.

Patients with a wash-in of at least 365 days between the first prescription for a glucose-lowering medication and the later of the patient registration date and the up-to-standard date of their practice were included in a survival analysis comparing the risk of all-cause mortality by year of onset of treated type 2 diabetes.

5.2.3. Calculation of diabetes prevalence

The date of diabetes presentation was taken as the earlier of the first diagnosis of diabetes or the first prescription for a medicine used to lower blood glucose. Patients with secondary diabetes were excluded from the study. Patients were classed as a prevalent case from the later of their date of diabetes presentation and their practice's up-to-standard date until their censor date (defined as the earliest of their transfer-out date or date of death, if applicable, and the end of the study period).

Table 5.1 Decisions rules implemented to assign a diagnosis of type 1 or type 2 diabetes to people with diabetes

Rule	T1	T2	T0	Insulin	GLT	Age	BMI	Diabetes type	HbA_{1c}	Notes
1	1[a]	1		1	0	31–39	<=25	1		
2	1[a]	1		1	0	<=30		1		
3	1[a]	0		1	0			1		
4	IDDM (no T1)	0		1	0	31–39	<=25	1		
5	IDDM (no T1)	0		1	0	<=30		1		
6	1[a]	0		0	0	<=30		1		
7	1[a]	0		0	0	31–39	<=25	1		
8	0	0		1	0	<=30		1		
9	0	0		1	0	31–39	<=25	1		
10	1	1		0	0			2		
11	0	0	1	0	Met			2		Must have >=1 t0 diagnostic code
11y[b]	0	0	1	0	Met			2	>=6.5%	T0 non-diagnostic codes only
12	0	0	1	0	0			2		Must have >=1 t0 diagnostic code
12y[c]	0	0	1	0	0			2	>=6.5%	T0 non-diagnostic codes only
13					GLT (non-met)			2		
14	0	1			0			2		

Rule	T1	T2	T0	Insulin	GLT	Age	BMI	Diabetes type	HbA_{1c}	Notes
15		1			Met			2		
16	0	0		1	0	>=40		DM		
17	0	0		1	0	31–39 or is null	>25 or is null	DM		
18	IDDM (no T1)	0		1	0	31–39	>25 or null	DM		
19	IDDM (no T1)	0		1	0	>=40 or null		DM		
20	1	0			Met			DM		
21	0	0		1	Met			DM		
22	1	0		0	0			DM		Remainder (not rule 6 or 7)
23	1	1		1	0			DM		Remainder (not rule 1 or 2)
11x	0	0	1	0	Met			Not DM	None or <6.5%	T0 non-diagnostic codes only
12x	0	0	1	0	0			Not DM	None or <6.5%	T0 non-diagnostic codes only
24	0	0	0	0	0/Met			Not DM		

[a] Must have at least one non-IDDM T1 code

[b] Include these rules as a sensitivity analysis only

Met = metformin, GLT = glucose-lowering therapy, T1 = type 1 diabetes, T2 = type 2 diabetes, T0 = unspecified diabetes type, GLT = glucose-lowering therapy

The method used to calculate point prevalence was similar to that used in censuses. Patients having a diabetes presentation date prior to the mid-year point (30th June) and a censor date after that mid-year point were included as a prevalent case in that year regardless of their duration of diabetes. Crude prevalence was calculated by dividing the number of people with diabetes in CPRD at the mid-year point of each year from 1991 to 2013 by the total number of patients who were alive and registered at an up-to-standard practice on the same date. Age- and sex- standardised prevalence rates were also calculated using 1991 as the reference year.

Age- and sex-stratified prevalence of type 1 and type 2 diabetes was multiplied by the total UK population from data from the ONS[428] to produce an estimate of the number of people with diabetes in the UK.

The prevalence of type 2 diabetes by treatment type was calculated by dividing the number of patients with type 2 diabetes using each type of glucose-lowering medication (insulin or oral glucose-lowering medicines and GLP-1 agonists) by the total number of patients with a registered status in CPRD at the mid-year point. The index date was taken as the date of the patient's first prescription for glucose-lowering medication or insulin, which needed to occur prior to the mid-year point. An in-house application was used to reconcile periods of combined exposure to multiple glucose-lowering therapies. A gap longer than 90 days between prescriptions for the same glucose-lowering medication was used to indicate discontinuation of that treatment. The end of the course of therapy was taken as the last prescription date plus 30 days. However, as type 2 diabetes is a chronic progressive condition, it is unusual for patients to discontinue therapy. Therefore, for patients who had previously received prescriptions for glucose-lowering medication but no glucose-lowering regimen

identified at the mid-year point, the last observed glucose-lowering regimen was carried forward. Diet-controlled patients were identified if they had type 2 diabetes but had received no prescriptions for a glucose-lowering medication prior to the mid-year point.

5.2.4. Statistical analysis

Wilson (or score) 95% confidence intervals were calculated for prevalence rates. The number of people with diabetes in the UK was projected for the year 2020 by fitting a linear regression line to the estimates for the years between 2000 and 2013.

For the survival analysis, time to death was evaluated for incident cases of type 1 diabetes or treated type 2 diabetes using the Cox proportional hazards model, adjusted for index, age and sex. Patients were followed to their censor date. The proportional hazards assumption was tested by examining the Pearson correlation between Schoenfeld residuals and the rank of survival time for cases that had progressed to death. The proportional hazards assumption was also tested using interactions between the covariates and time. aHRs are presented with the 95% confidence intervals. Analyses were carried out using Microsoft Excel and IBM SPSS Statistics version 20.

5.2.5. Sensitivity analyses

A sensitivity analysis was carried out using only those patients whose records were eligible for linkage to HES data from 1997 to 2011. Here, prevalent cases of diabetes were identified from diagnoses recorded in either HES or CPRD GOLD and from

prescriptions recorded in CPRD GOLD. Classification of diabetes type was also determined using data from both the CPRD and HES sources. The denominator data was restricted to patients in CPRD who were HES eligible.

In a separate sensitivity analysis, the percentage of patients with diabetes of unknown type was calculated for each GP practice contributing data to CPRD and the prevalence of diabetes by year was then calculated using only those patients registered at a practice with ≤1% and ≤2% of diabetes patients having an unknown type.

5.3. Results

5.3.1. Patient demographics

The demographic characteristics of people with diabetes are detailed in Table 5.2. Overall, the mean age of the prevalent population of people with diabetes increased from 62.9 years to 64.8 years between 1991 and 2013 and the percentage of males increased from 52% to 56% during this period. For people with type 1 diabetes, the age of the prevalent population increased from 35.8 years in 19991 to 38.6 years in 2013 and the duration of diagnosed diabetes increased from 14.5 years to 15.5 years during this period. For type 2 diabetes, the age of the prevalent population decreased from 66.9 years in 1991 to 66.8 years in 2013 while the duration of diabetes increased from 4.3 years to7.2 years.

5.3.2. Crude prevalence of diabetes

The crude prevalence of diagnosed type 1 diabetes increased from 0.19% (95% CI 0.18%–0.19%) to 0.32% (0.31%–0.32%) between 1991 and 2013, and the crude prevalence of diagnosed type 2 diabetes increased year on year from 1.32% (1.30%–1.34%) to 4.54% (4.52%–4.56%) during the same period (Table 5.3). The combined crude prevalence of diagnosed type 1 and type 2 diabetes increased from 1.66% (1.64%–1.69%) in 1991 to 4.94% (4.92%–4.96%) in 2013.

Table 5.2 Patient Demographics

Parameter	Year											
	1991		1995		2000		2005		2010		2013	
Type 1 diabetes												
Prevalent cases, n	2,006		3,319		8,162		13,339		14,575		13,978	
Males, n (%)	1,100	(55%)	1,918	(58%)	4,756	(58%)	7,792	(58%)	8,580	(59%)	8,205	(59%)
Age, mean (median), years	35.8	(34.0)	37.3	(35.0)	38.3	(37.0)	39.2	(39.0)	39.0	(39.0)	38.6	(39.0)
Diabetes duration, median (IQR), years[a]	14.5	(6.3–23.5)	15.3	(6.4-24.5)	14.5	(6.5-25.5)	14.7	(6.2-26.5)	15.5	(6.9-27.5)	15.5	(7.0-27.9)
BMI, mean (SD), kg/m2[b]	24.4	(3.3)	24.7	(3.6)	25.3	(4.1)	25.4	(4.5)	25.5	(4.7)	25.4	(4.8)
Weight, mean (SD), kg[b]	69.8	(13.2)	71.6	(13.4)	72.8	(15.2)	73.1	(17.3)	73.5	(18)	73.1	(18.4)
Systolic BP, mean (SD), mmHg[b]	131.3	(20.6)	131.5	(19.7)	131.3	(19.1)	128.6	(17.3)	126.9	(16.3)	126.2	(15.7)
Total cholesterol, mean (SD), mmol/l[b]	6.0	(2.0)	5.4	(1.2)	5.1	(1.1)	4.7	(1.0)	4.6	(1.0)	4.6	(1.0)
Serum creatinine, mean (SD), µmol/l[b]	100.1	(66.8)	93.7	(32.7)	93.5	(42.2)	91.7	(43.0)	83.9	(41.2)	81.3	(39.0)
Smoking status												
non-smoker, n (%)	1,148	(57%)	1,962	(59%)	4,692	(57%)	7,697	(58%)	8,232	(56%)	7,626	(55%)
ex-smoker, n (%)	122	(6%)	320	(10%)	948	(12%)	2,202	(17%)	2,627	(18%)	2,501	(18%)
current smoker, n (%)	512	(26%)	831	(25%)	2,135	(26%)	3,044	(23%)	3,027	(21%)	2,710	(19%)
Charlson Index, median (IQR)[c]	1.0	(1.0-2.0)	1.0	(1.0-2.0)	1.0	(1.0-2.0)	2.0	(1.0-2.0)	2.0	(1.0-2.0)	2.0	(1.0-3.0)
Antihypertensive therapy, n (%)[d]	224	(11%)	489	(15%)	1,790	(22%)	4,361	(33%)	4,736	(32%)	4,167	(30%)
Lipid-lowering therapy, n (%)[d]	18	(1%)	68	(2%)	681	(8%)	4,529	(34%)	5,616	(39%)	4,958	(35%)
Antiplatelet therapy, n (%)[d]	56	(3%)	169	(5%)	730	(9%)	2,848	(21%)	2,812	(19%)	2,141	(15%)
Prior cancer, n (%)[c]	25	(1%)	59	(2%)	169	(2%)	380	(3%)	489	(3%)	511	(4%)
Prior large vessel disease, n (%)[c]	71	(4%)	167	(5%)	456	(6%)	877	(7%)	911	(6%)	845	(6%)
Prior visual problems, n (%)[c]	404	(20%)	896	(27%)	2,453	(30%)	5,107	(38%)	7,547	(52%)	7,650	(55%)

	1991		1995		2000		2005		2010		2013	
Type 2 diabetes												
Prevalent cases, n	14,202		26,773		76,531		155,936		201,554		200,957	
Males, n (%)	7,422	(52%)	14,121	(53%)	41,104	(54%)	85,085	(55%)	112,008	(56%)	112,822	(56%)
Age, mean (median), years	66.9	(68.0)	66.8	(68.0)	66.4	(68.0)	66.2	(67.0)	66.6	(67.0)	66.8	(68.0)
Diabetes duration, median (IQR), years[a]	4.3	(1.5-8.8)	4.6	(2.1-9.2)	5.0	(2.0-9.5)	4.6	(2.2-9.3)	6.3	(2.9-10.4)	7.2	(3.4-11.7)
BMI, mean (SD), kg/m2[b]	27.9	(5.1)	28.4	(5.2)	29.3	(5.4)	30.1	(5.8)	30.8	(6.0)	30.7	(6.0)
Weight, mean (SD), kg[b]	77.3	(16.2)	79.0	(16.4)	82.2	(17.5)	84.9	(18.8)	87.1	(19.5)	87.2	(19.6)
Systolic BP, mean (SD), mmHg[b]	149.0	(22.0)	147.0	(20.0)	145.0	(19.0)	137.4	(16.9)	134.0	(16.0)	133.0	(15.0)
Total cholesterol, mean (SD), mmol/l[b]	6.3	(1.3)	5.9	(1.3)	5.3	(1.1)	4.5	(1.1)	4.3	(1.1)	4.3	(1.1)
Serum creatinine, mean (SD), µmol/l[b]	90.8	(26.9)	99.2	(33.0)	97.6	(33.3)	95.5	(34.0)	89.4	(35.5)	87.8	(35.8)
Smoking status[e]												
non-smoker, n (%)	8,198	(58%)	1,6114	(60%)	41,337	(54%)	76,442	(49%)	97,602	(48%)	99,885	(50%)
ex-smoker, n (%)	1,428	(10%)	4,331	(16%)	19,110	(25%)	55,520	(36%)	74,999	(37%)	72,808	(36%)
current smoker, n (%)	2,384	(17%)	4,577	(17%)	13,820	(18%)	23,404	(15%)	28,639	(14%)	27,850	(14%)
Charlson Index, median (IQR)[c]	1.0	(1.0-2.0)	2.0	(1.0-2.0)	2.0	(1.0-3.0)	2.0	(1.0-3.0)	2.0	(1.0-4.0)	2.0	(1.0-4.0)
Antihypertensive therapy, n (%)[d]	5,157	(36%)	11,742	(44%)	44,549	(58%)	117,114	(75%)	154,302	(77%)	150,873	(75%)
Lipid-lowering therapy, n (%)[d]	303	(2%)	1,300	(5%)	18,046	(24%)	109,022	(70%)	157,346	(78%)	153,666	(76%)
Antiplatelet therapy, n (%)[d]	1,622	(11%)	5,223	(20%)	24,242	(32%)	80,006	(51%)	95,972	(48%)	78,307	(39%)
Prior cancer, n (%)[c]	730	(5%)	1,728	(6%)	5,575	(7%)	14,586	(9%)	23,318	(12%)	25,765	(13%)
Prior large vessel disease, n (%)[c]	2,965	(21%)	6,619	(25%)	19,128	(25%)	39,967	(26%)	48,177	(24%)	46,175	(23%)
Prior visual problems, n (%)[c]	2,339	(16%)	6,456	(24%)	20,605	(27%)	51,005	(33%)	88,462	(44%)	95,543	(48%)

[a] Time between diabetes presentation date and mid year point (30/06).

[b] The nearest record within the specific year, searching in the following order: 30 days prior, 30 days after, 180 days prior and then 184 days after the index date.

[c] Based on diagnoses recorded prior to the mid year point (30/06).

[d] Presence of one or more prescriptions for drug class in the specific year.

[e] Nearest recorded smoking status prior to the mid year point (30/06). If no diagnosis is recorded prior to the mid year point, the nearest recoded smoking status after mid year point was used.

Table 5.3 Crude prevalence of diagnosed diabetes between 1991 and 2013

Year	CPRD population	Type 1 diabetes			Type 2 diabetes			Diabetes of unknown type			Type 1 and type 2 diabetes		
		Cases	Prevalence (95%CI)		Cases	Prevalence (95%CI)		Cases	Prevalence (95%CI)		Cases	Prevalence (95%CI)	
1991	1,076,146	2,006	0.19%	(0.18%–0.19%)	14,202	1.32%	(1.30%–1.34%)	1,706	0.16%	(0.15%–0.17%)	17,914	1.66%	(1.64%–1.69%)
1992	1,191,397	2,292	0.19%	(0.18%–0.20%)	17,028	1.43%	(1.41%–1.45%)	1,798	0.15%	(0.14%–0.16%)	21,118	1.77%	(1.75%–1.80%)
1993	1,371,781	2,687	0.20%	(0.19%–0.20%)	20,708	1.51%	(1.49%–1.53%)	2,055	0.15%	(0.14%–0.16%)	25,450	1.86%	(1.83%–1.88%)
1994	1,490,222	3,024	0.20%	(0.20%–0.21%)	23,621	1.59%	(1.57%–1.61%)	2,122	0.14%	(0.14%–0.15%)	28,767	1.93%	(1.91%–1.95%)
1995	1,601,020	3,319	0.21%	(0.20%–0.21%)	26,773	1.67%	(1.65%–1.69%)	2,204	0.14%	(0.13%–0.14%)	32,296	2.02%	(2.00%–2.04%)
1996	1,816,415	3,881	0.21%	(0.21%–0.22%)	31,905	1.76%	(1.74%–1.78%)	2,417	0.13%	(0.13%–0.14%)	38,203	2.10%	(2.08%–2.12%)
1997	2,107,577	4,555	0.22%	(0.21%–0.22%)	38,292	1.82%	(1.80%–1.83%)	2,646	0.13%	(0.12%–0.13%)	45,493	2.16%	(2.14%–2.18%)
1998	2,409,111	5,279	0.22%	(0.21%–0.23%)	46,426	1.93%	(1.91%–1.94%)	3,041	0.13%	(0.12%–0.13%)	54,746	2.27%	(2.25%–2.29%)
1999	2,853,992	6,468	0.23%	(0.22%–0.23%)	58,231	2.04%	(2.02%–2.06%)	3,487	0.12%	(0.12%–0.13%)	68,186	2.39%	(2.37%–2.41%)
2000	3,516,695	8,162	0.23%	(0.23%–0.24%)	76,531	2.18%	(2.16%–2.19%)	4,252	0.12%	(0.12%–0.12%)	88,945	2.53%	(2.51%–2.55%)
2001	3,805,202	9,252	0.24%	(0.24%–0.25%)	90,886	2.39%	(2.37%–2.40%)	4,438	0.12%	(0.11%–0.12%)	104,576	2.75%	(2.73%–2.76%)
2002	4,245,243	10,684	0.25%	(0.25%–0.26%)	110,861	2.61%	(2.60%–2.63%)	4,685	0.11%	(0.11%–0.11%)	126,230	2.97%	(2.96%–2.99%)
2003	4,445,520	11,647	0.26%	(0.26%–0.27%)	125,848	2.83%	(2.82%–2.85%)	4,595	0.10%	(0.10%–0.11%)	142,090	3.20%	(3.18%–3.21%)
2004	4,663,313	12,579	0.27%	(0.27%–0.27%)	142,333	3.05%	(3.04%–3.07%)	4,489	0.10%	(0.09%–0.10%)	159,401	3.42%	(3.40%–3.43%)
2005	4,784,550	13,339	0.28%	(0.27%–0.28%)	155,936	3.26%	(3.24%–3.28%)	4,267	0.09%	(0.09%–0.09%)	173,542	3.63%	(3.61%–3.64%)
2006	4,811,131	13,790	0.29%	(0.28%–0.29%)	166,751	3.47%	(3.45%–3.48%)	4,045	0.08%	(0.08%–0.09%)	184,586	3.84%	(3.82%–3.85%)
2007	4,869,132	14,118	0.29%	(0.29%–0.29%)	177,256	3.64%	(3.62%–3.66%)	4,013	0.08%	(0.08%–0.09%)	195,387	4.01%	(4.00%–4.03%)
2008	4,880,882	14,326	0.29%	(0.29%–0.30%)	186,700	3.83%	(3.81%–3.84%)	4,021	0.08%	(0.08%–0.08%)	205,047	4.20%	(4.18%–4.22%)
2009	4,885,729	14,574	0.30%	(0.29%–0.30%)	195,180	3.99%	(3.98%–4.01%)	3,983	0.08%	(0.08%–0.08%)	213,737	4.37%	(4.36%–4.39%)
2010	4,825,358	14,575	0.30%	(0.30%–0.31%)	201,554	4.18%	(4.16%–4.19%)	3,887	0.08%	(0.08%–0.08%)	220,016	4.56%	(4.54%–4.58%)
2011	4,763,251	14,563	0.31%	(0.30%–0.31%)	206,633	4.34%	(4.32%–4.36%)	3,858	0.08%	(0.08%–0.08%)	225,054	4.72%	(4.71%–4.74%)
2012	4,676,468	14,523	0.31%	(0.31%–0.32%)	208,616	4.46%	(4.44%–4.48%)	3,760	0.08%	(0.08%–0.08%)	226,899	4.85%	(4.83%–4.87%)
2013	4,425,503	13,978	0.32%	(0.31%–0.32%)	200,957	4.54%	(4.52%–4.56%)	3,574	0.08%	(0.08%–0.08%)	218,509	4.94%	(4.92%–4.96%)

Selecting only those practices in which ≤1% of diabetes patients are of unknown diabetes type, the prevalence of type 1 and type 2 diabetes increased from 0.31% (0.29%–0.34%) and 2.95% (2.87%–3.03%) in 2003 (where there was a sufficiently large population) to 0.32% (0.31%–0.33%) and 4.61% (4.56%–4.65%) in 2013, respectively (Table 5.4a). Selecting only those practices where ≤2% of diabetes patients were of unknown diabetes type, the prevalence of type 1 and type 2 diabetes increased from 0.29% (0.28%–0.30%) and 2.94% (2.91%–2.98%) in 2003 to 0.32% (0.31%–0.32%) and 4.66% (4.63%–4.68%) in 2013, respectively (Table 5.4b).

For those patients who were HES-eligible, the prevalence of type 1 and type 2 diabetes increased from 0.17% (0.16%–0.18%) and 1.84% (1.82%–1.87%) in 1997 to 0.23% (0.22%–0.23%) and 4.40% (4.37%–4.42%) in 2011 (Table 5.5). During the same period, the overall prevalence of diabetes increased from 2.16% (2.13%–2.19%) to 4.75% (4.72%–4.77%).

5.3.3. Prevalence of diabetes by age

For 6 selected calendar years (1991, 1995, 2000, 2005, 2010 and 2013), the prevalence of diabetes increased with increasing calendar year for age groups above the age of 25 (Figure 5.1a). The prevalence of diabetes increased with increasing age group until the age of 70–84 years, depending on study year (the highest prevalence rates were in the 75–79 age group in 1991, 2005, 2010 and 2013, the 70–74 age group in 2000 and the 80–84 age group in 1995). The prevalence rates of type 1 diabetes, type 2 diabetes and treated type 2 diabetes by age group and calendar year are shown in Figure 5.1b, c and d.

Table 5.4 Prevalence of type 1 and type 2 diabetes in practices where less than a) 1% and b) 2% of patients have unknown diabetes type

a)

Year	Type 1 diabetes			Type 2 diabetes			Patients registered at selected practices	
	Number of cases	Prevalence (95% CI)		Number of cases	Prevalence		Number of patients	% of total CPRD population
1993	13	0.20%	(0.12%–0.34%)	124	1.87%	(1.57%–2.23%)	6,629	0.48%
1994	7	0.18%	(0.09%–0.36%)	61	1.53%	(1.19%–1.95%)	4,000	0.27%
1995	27	0.15%	(0.10%–0.22%)	327	1.81%	(1.63%–2.02%)	18,030	1.13%
1996	51	0.23%	(0.18%–0.30%)	328	1.49%	(1.34%–1.66%)	22,021	1.21%
1997	18	0.22%	(0.14%–0.34%)	145	1.75%	(1.49%–2.06%)	82,74	0.39%
1998	38	0.23%	(0.17%–0.31%)	288	1.73%	(1.55%–1.94%)	16,608	0.69%
1999	87	0.26%	(0.21%–0.32%)	729	2.19%	(2.04%–2.36%)	33,229	1.16%
2000	122	0.30%	(0.25%–0.36%)	910	2.22%	(2.08%–2.36%)	41,049	1.17%
2001	193	0.28%	(0.24%–0.32%)	1,675	2.41%	(2.30%–2.52%)	69,573	1.83%
2002	260	0.27%	(0.24%–0.31%)	2,469	2.61%	(2.51%–2.71%)	94,700	2.23%
2003	542	0.31%	(0.29%–0.34%)	5,109	2.95%	(2.87%–3.03%)	172,976	3.89%
2004	882	0.29%	(0.27%–0.31%)	9,523	3.13%	(3.07%–3.20%)	303,804	6.51%
2005	1,287	0.29%	(0.28%–0.31%)	14,499	3.32%	(3.26%–3.37%)	437,334	9.14%
2006	1,604	0.31%	(0.30%–0.33%)	18,406	3.57%	(3.52%–3.62%)	516,189	10.73%
2007	1,785	0.31%	(0.30%–0.33%)	21,230	3.71%	(3.67%–3.76%)	571,614	11.74%
2008	2,078	0.31%	(0.30%–0.32%)	25,737	3.84%	(3.80%–3.89%)	669,781	13.72%
2009	2,548	0.31%	(0.30%–0.33%)	32,865	4.04%	(4.00%–4.08%)	813,834	16.66%
2010	2,741	0.31%	(0.30%–0.33%)	37,766	4.31%	(4.26%–4.35%)	876,804	18.17%
2011	2,876	0.32%	(0.31%–0.33%)	40,291	4.43%	(4.39%–4.48%)	908,758	19.08%
2012	3,084	0.32%	(0.31%–0.33%)	43,196	4.47%	(4.43%–4.51%)	966,597	20.67%
2013	2,895	0.32%	(0.31%–0.33%)	41,489	4.61%	(4.56%–4.65%)	900,566	20.35%

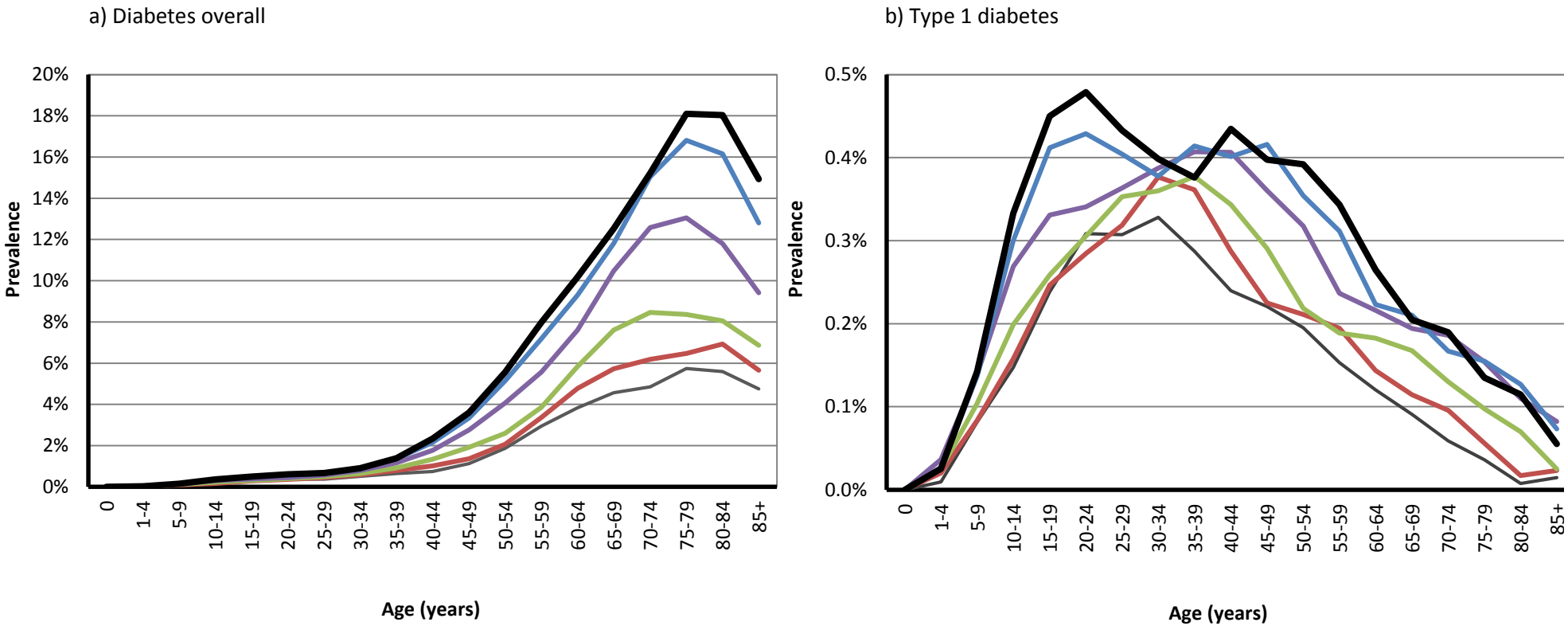
b)

Year	Type 1 diabetes			Type 2 diabetes			Patients registered at selected practices	
	Number of cases	Prevalence (95% CI)		Number of cases	Prevalence		Number of patients	% of total CPRD population
1991	4	0.09%	(0.03%–0.23%)	95	2.13%	(1.74%–2.60%)	4,463	0.41%
1992	11	0.10%	(0.05%–0.17%)	169	1.49%	(1.28%–1.73%)	11,339	0.95%
1993	21	0.15%	(0.10%–0.23%)	201	1.47%	(1.28%–1.69%)	13,664	1.00%
1994	67	0.18%	(0.14%–0.23%)	606	1.65%	(1.52%–1.78%)	36,754	2.47%
1995	80	0.20%	(0.16%–0.25%)	665	1.65%	(1.53%–1.77%)	40,407	2.52%
1996	78	0.21%	(0.17%–0.26%)	625	1.69%	(1.57%–1.83%)	36,919	2.03%
1997	149	0.22%	(0.19%–0.26%)	1,297	1.92%	(1.82%–2.03%)	67,451	3.20%
1998	189	0.23%	(0.20%–0.27%)	1,530	1.87%	(1.78%–1.96%)	81,882	3.40%
1999	330	0.24%	(0.21%–0.26%)	2,881	2.05%	(1.98%–2.13%)	140,417	4.92%
2000	504	0.24%	(0.22%–0.27%)	4,703	2.27%	(2.21%–2.33%)	207,275	5.89%
2001	935	0.26%	(0.24%–0.27%)	8,990	2.45%	(2.40%–2.51%)	366,268	9.63%
2002	1,605	0.27%	(0.26%–0.28%)	16,107	2.71%	(2.66%–2.75%)	595,327	14.02%
2003	2,691	0.29%	(0.28%–0.30%)	27,668	2.94%	(2.91%–2.98%)	940,878	21.16%
2004	3,844	0.29%	(0.28%–0.29%)	42,941	3.19%	(3.16%–3.22%)	1,346,903	28.88%
2005	5,438	0.29%	(0.28%–0.30%)	62,662	3.37%	(3.34%–3.39%)	1,861,091	38.90%
2006	6,720	0.30%	(0.29%–0.31%)	80,109	3.59%	(3.57%–3.62%)	2,229,994	46.35%
2007	7,756	0.30%	(0.29%–0.31%)	96,309	3.74%	(3.71%–3.76%)	2,577,913	52.94%
2008	8,065	0.30%	(0.29%–0.31%)	105,721	3.94%	(3.92%–3.96%)	2,683,005	54.97%
2009	8,657	0.30%	(0.30%–0.31%)	116,691	4.10%	(4.08%–4.12%)	2,846,883	58.27%
2010	9,426	0.31%	(0.30%–0.31%)	129,684	4.22%	(4.20%–4.25%)	3,070,251	63.63%
2011	9,799	0.31%	(0.30%–0.32%)	139,197	4.42%	(4.39%–4.44%)	3,152,629	66.19%
2012	9,797	0.31%	(0.31%–0.32%)	142,604	4.53%	(4.51%–4.55%)	3,149,316	67.34%
2013	9,914	0.32%	(0.31%–0.32%)	145,193	4.66%	(4.63%–4.68%)	3,118,196	70.46%

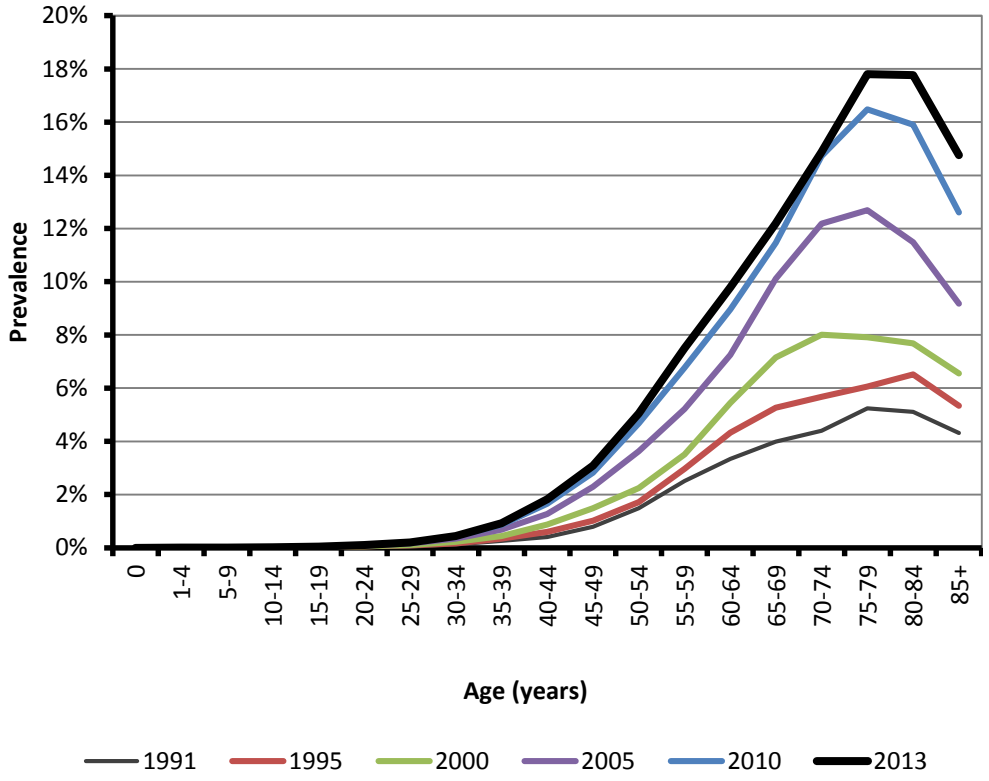
Table 5.5 Prevalence of diabetes in HES eligible patients

Year	CPRD population	Type 1 diabetes			Type 2 diabetes			Diabetes of unknown type			Type 1 and type 2 diabetes		
		Cases	Prevalence (95% CI)		Cases	Prevalence (95% CI)		Cases	Prevalence (95% CI)		Cases	Prevalence (95% CI)	
1997	1,249,523	2,117	0.17%	(0.16%–0.18%)	23,012	1.84%	(1.82%–1.87%)	1,864	0.15%	(0.14%–0.16%)	26,993	2.16%	(2.13%–2.19%)
1998	1,403,674	2,410	0.17%	(0.16%–0.18%)	27,536	1.96%	(1.94%–1.98%)	2,105	0.15%	(0.14%–0.16%)	32,051	2.28%	(2.26%–2.31%)
1999	1,701,659	2,964	0.17%	(0.17%–0.18%)	35,162	2.07%	(2.05%–2.09%)	2,468	0.15%	(0.14%–0.15%)	40,594	2.39%	(2.36%–2.41%)
2000	2,150,872	3,774	0.18%	(0.17%–0.18%)	47,322	2.20%	(2.18%–2.22%)	3,149	0.15%	(0.14%–0.15%)	54,245	2.52%	(2.50%–2.54%)
2001	2,309,587	4,167	0.18%	(0.18%–0.19%)	56,097	2.43%	(2.41%–2.45%)	3,404	0.15%	(0.14%–0.15%)	63,668	2.76%	(2.74%–2.78%)
2002	2,536,073	4,632	0.18%	(0.18%–0.19%)	67,575	2.66%	(2.64%–2.68%)	3,718	0.15%	(0.14%–0.15%)	75,925	2.99%	(2.97%–3.01%)
2003	2,630,665	4,987	0.19%	(0.18%–0.19%)	76,073	2.89%	(2.87%–2.91%)	3,814	0.14%	(0.14%–0.15%)	84,874	3.23%	(3.21%–3.25%)
2004	2,718,426	5,235	0.19%	(0.19%–0.20%)	84,540	3.11%	(3.09%–3.13%)	3,862	0.14%	(0.14%–0.15%)	93,637	3.44%	(3.42%–3.47%)
2005	2,801,441	5,602	0.20%	(0.19%–0.21%)	92,954	3.32%	(3.30%–3.34%)	3,862	0.14%	(0.13%–0.14%)	102,418	3.66%	(3.63%–3.68%)
2006	2,857,959	5,889	0.21%	(0.20%–0.21%)	100,728	3.52%	(3.50%–3.55%)	3,850	0.13%	(0.13%–0.14%)	110,467	3.87%	(3.84%–3.89%)
2007	2,940,088	6,177	0.21%	(0.20%–0.22%)	108,331	3.68%	(3.66%–3.71%)	3,893	0.13%	(0.13%–0.14%)	118,401	4.03%	(4.00%–4.05%)
2008	2,933,958	6,266	0.21%	(0.21%–0.22%)	113,499	3.87%	(3.85%–3.89%)	3,854	0.13%	(0.13%–0.14%)	123,619	4.21%	(4.19%–4.24%)
2009	2,965,067	6,508	0.22%	(0.21%–0.22%)	119,521	4.03%	(4.01%–4.05%)	3,808	0.13%	(0.12%–0.13%)	129,837	4.38%	(4.36%–4.40%)
2010	2,940,780	6,611	0.22%	(0.22%–0.23%)	123,929	4.21%	(4.19%–4.24%)	3,699	0.13%	(0.12%–0.13%)	134,239	4.56%	(4.54%–4.59%)
2011	2,892,224	6,630	0.23%	(0.22%–0.23%)	127,119	4.40%	(4.37%–4.42%)	3,613	0.12%	(0.12%–0.13%)	137,362	4.75%	(4.72%–4.77%)

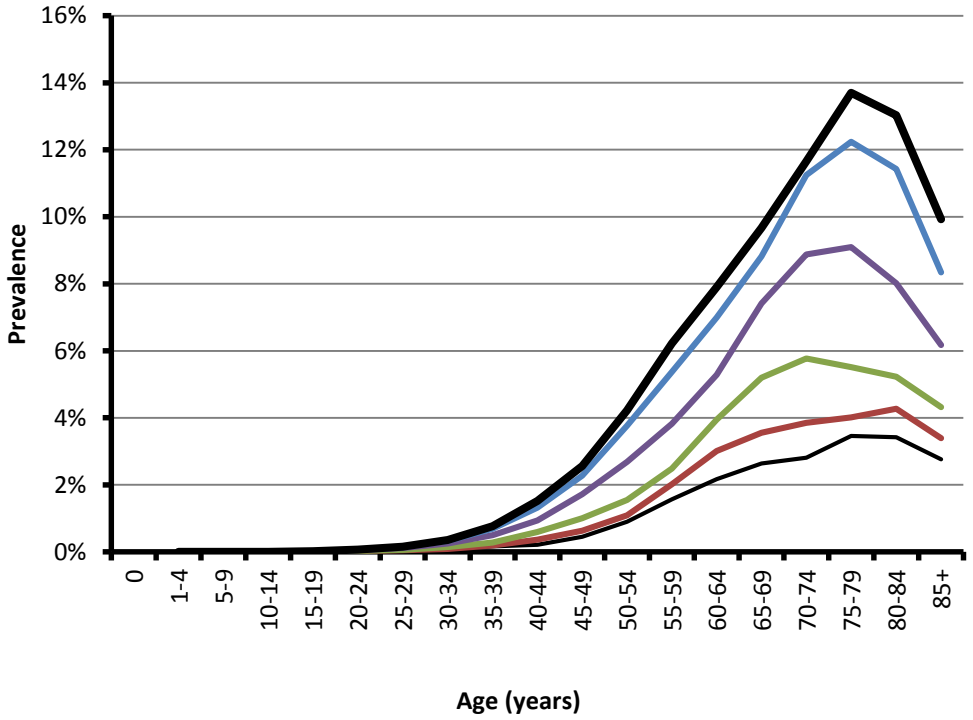
Figure 5.1 Prevalence of diabetes by age group



c) Type 2 diabetes



d) Type 2 diabetes treated with glucose-lowering medicines



In 1991, the prevalence of type 1 diabetes was highest between the ages of 30 and 34 years (0.33%, Figure 5.1b). By 2013, the highest prevalence of type 1 diabetes occurred between the ages of 20 and 24 years (0.48%).

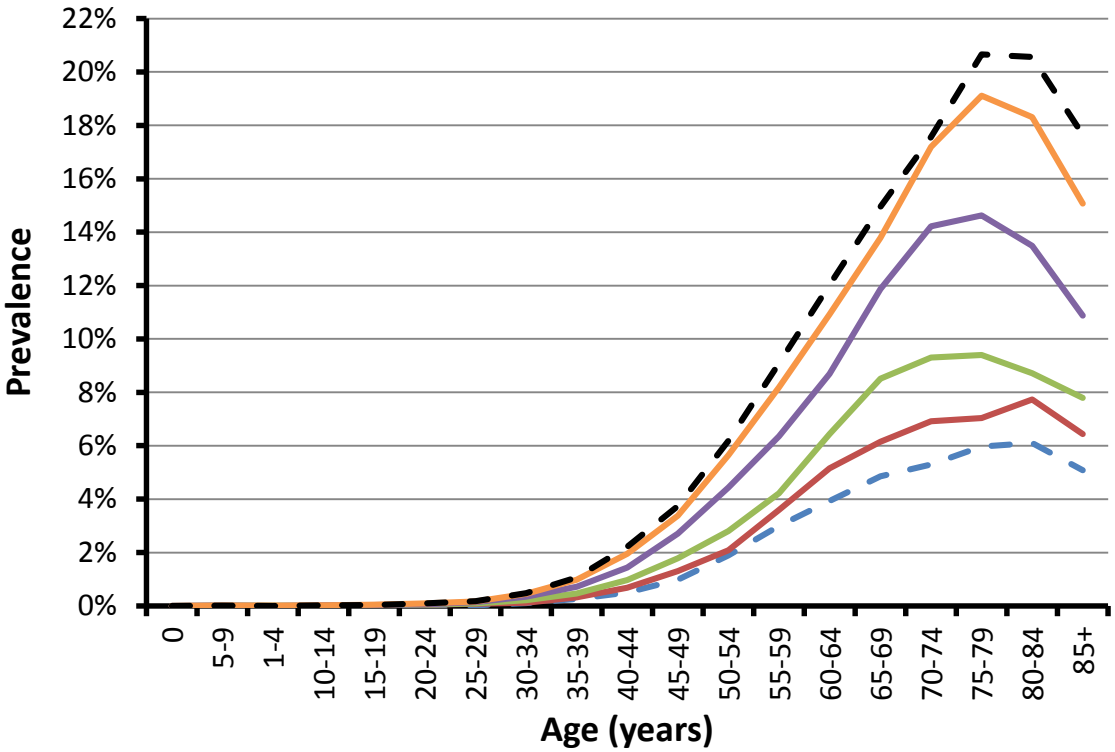
The crude prevalence of diagnosed type 2 diabetes increased each year for each age group and generally increased with increasing age group until 75–79 years of age in all years between 2000 and 2013 (Figure 5.1c). The crude prevalence of diagnosed type 2 diabetes was generally higher in males than females above the age of 40: in 1991 this was 2.94% (2.88%–3.01%) in males versus 2.34% (2.28%–2.40%) in females; in 2013, it was 9.95% (9.90%–10.01%) versus 7.29% (7.24%–7.33%), respectively (Figure 5.2). Below the age of 40, the crude prevalence of type 2 diabetes in males and females was similar: 0.06% (0.05%–0.07%) in males versus 0.08% (0.07%–0.09%) in females in 1991 and 0.25% (0.24%–0.26%) versus 0.22% (0.21%–0.22%) in 2013, respectively. Between 1992 and 1998, prevalence was highest in people aged 80–84; between 1999 and 2001, however, prevalence was highest in people aged 70–74.

5.3.4. Prevalence of type 2 diabetes by glucose-lowering regimen

The crude prevalence of people with diagnosed type 2 diabetes treated with insulin increased from 0.09% (95% CI 0.09%–0.10%) in 1991 to 0.67% (0.66%–0.68%) in 2013 (Figure 5.3). Over the same period, the prevalence of people with type 2 diabetes treated with glucose-lowering agents other than insulin and with diet and exercise also increased from 0.75% (0.73%–0.77%) and 0.48% (0.46%–0.49%) in 1991 to 2.89% (2.88%–2.91%) and 0.98% (0.97%–0.99%), respectively.

Figure 5.2 Prevalence of type 2 diabetes by age for a) males and b) females

a)



b)

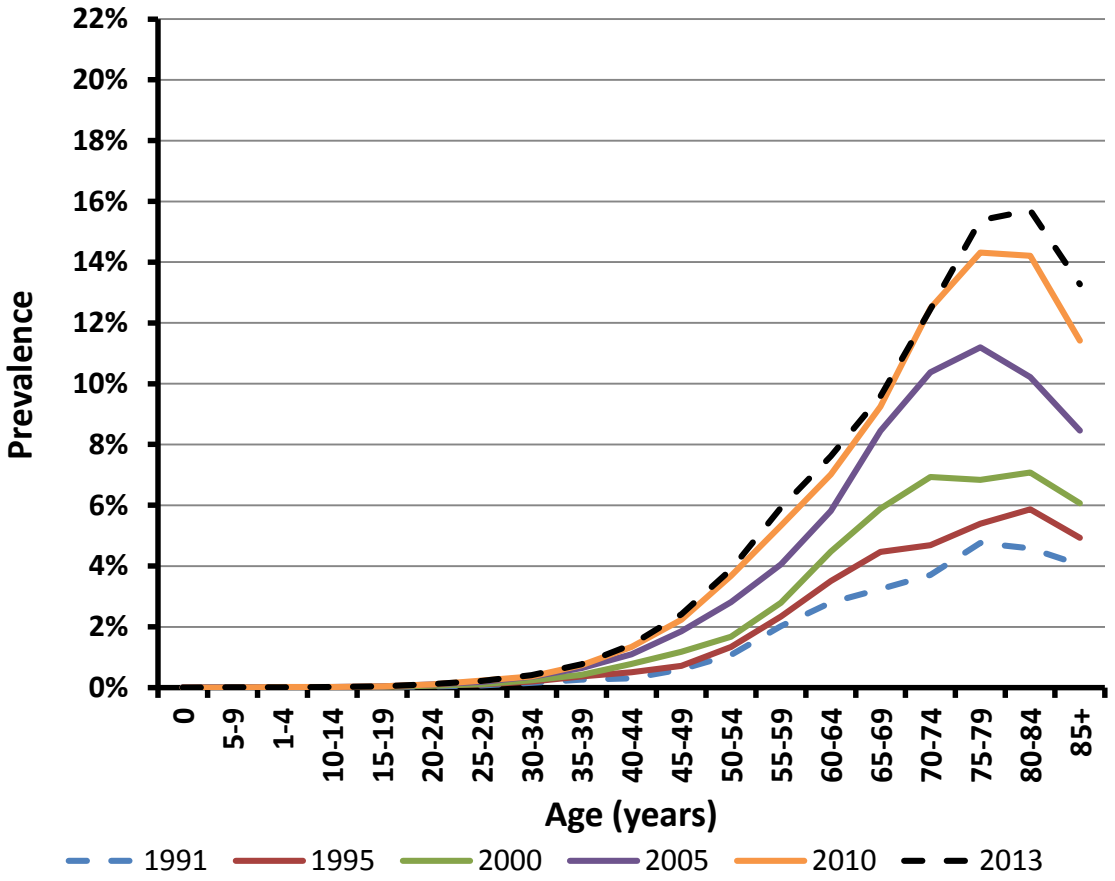
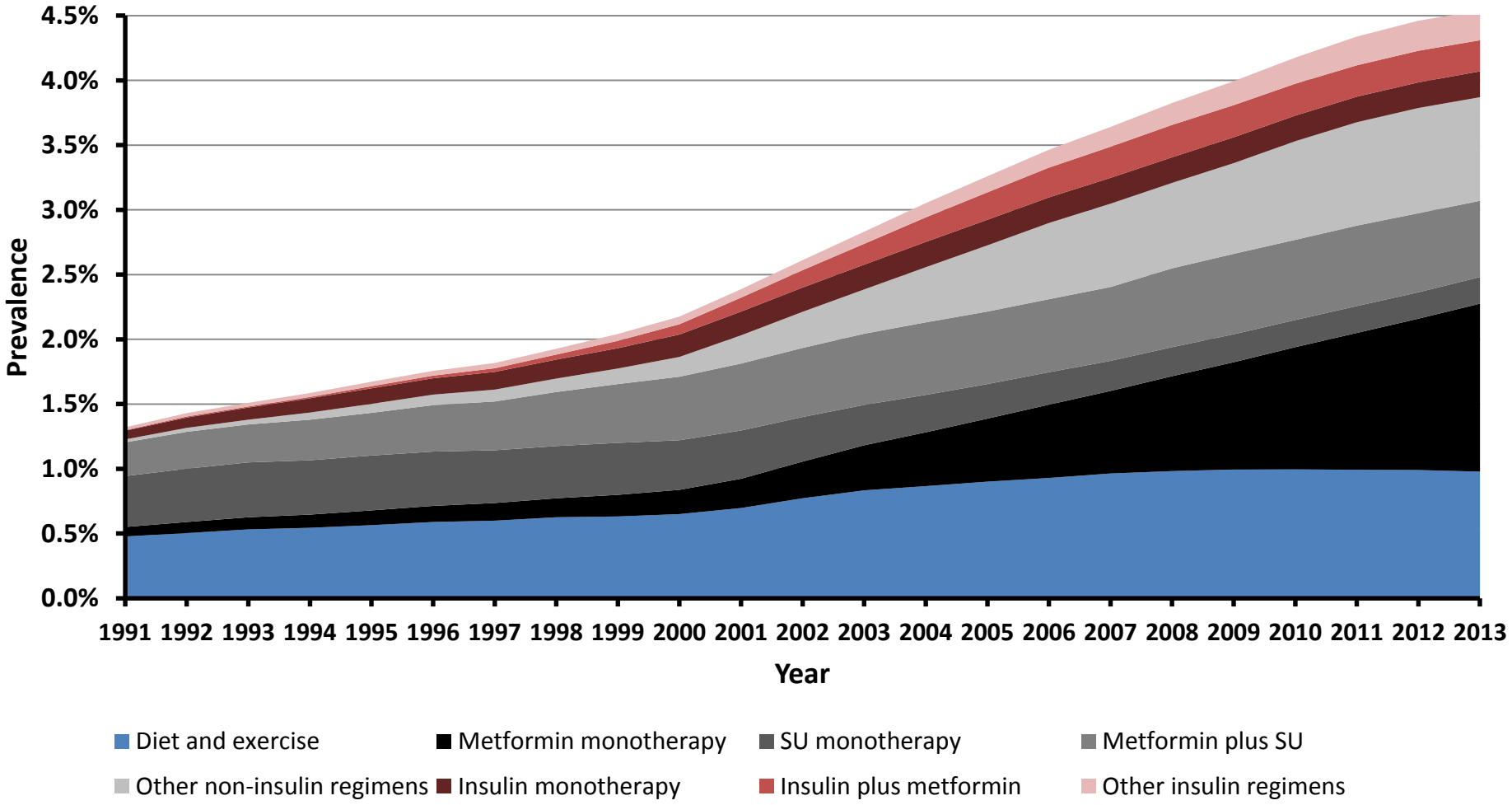


Figure 5.3 Prevalence of type 2 diabetes by treatment type



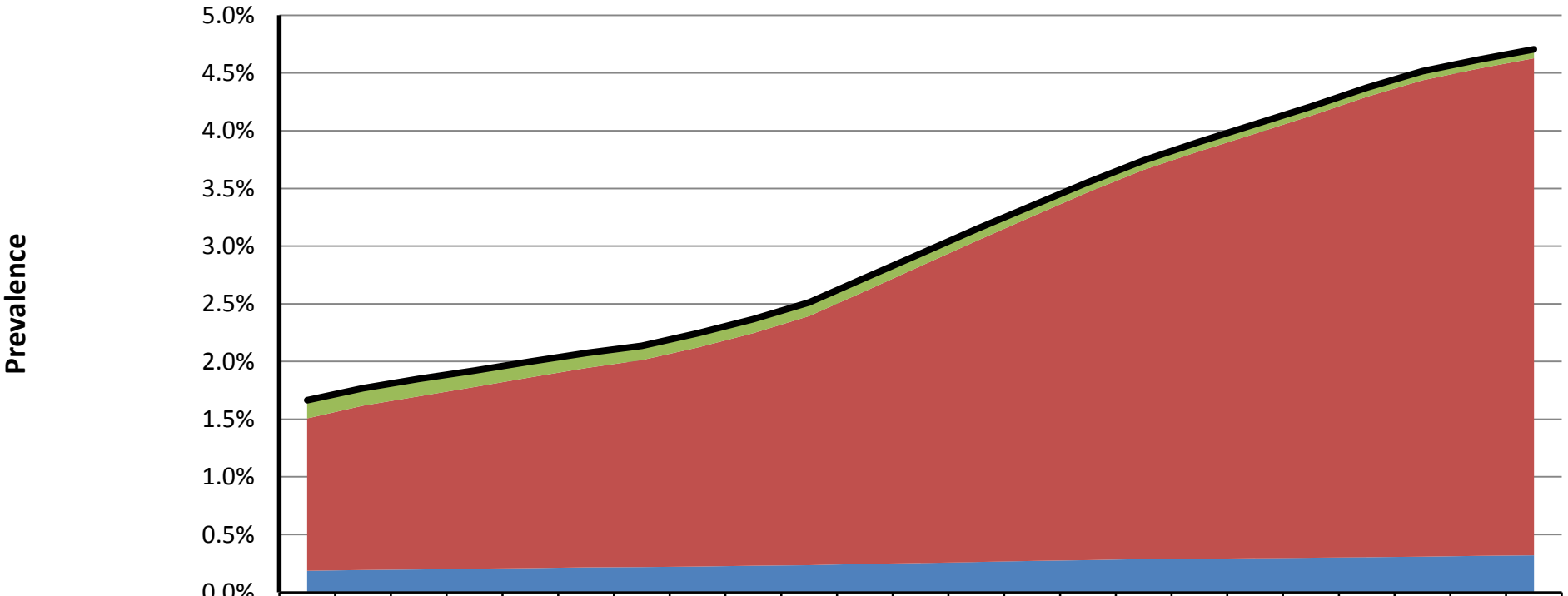
5.3.5. Age- and sex-standardised prevalence of diabetes

Age- and sex-standardised prevalence of type 1 and type 2 diabetes increased from 0.2% and 1.3% in 1991 to 0.3% and 4.3% in 2013, respectively (Figure 5.4). The corresponding figures for diabetes overall were 1.7% in 1991and 4.7% in 2013, respectively.

5.3.6. Estimated number of people in the UK with diabetes

The estimated number of people with diabetes in the UK increased year on year from 879,900 (879.9k) (95% CI 815.0k–952.7k) in 1991 to 3,060k (2,998k–3,124k) in 2013 (Figure 5.5 and Table 5.6). In 1991 there were 106.3k (95% CI 84.9k–136.1k) people with type 1 diabetes and 689.6k (639.4k–747.9k) people with type 2 diabetes. By 2013, this had increased to 201.6k (95% CI 184.0k–221.4k) people with type 1 diabetes and 2,808.3k (2,753.3k–2,865.3k) people with type 2 diabetes. By 2020, there will be a projected 4 million people with diabetes in the UK.

Figure 5.4 Age- and sex-standardised prevalence of diabetes (1991 = reference year)



	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Diabetes unknown type	0.2%	0.2%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
Type 2 diabetes	1.3%	1.4%	1.5%	1.6%	1.7%	1.7%	1.8%	1.9%	2.0%	2.2%	2.4%	2.6%	2.8%	3.0%	3.2%	3.4%	3.5%	3.7%	3.8%	4.0%	4.1%	4.2%	4.3%
Type 1 diabetes	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.2%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%	0.3%
Diabetes overall	1.7%	1.8%	1.8%	1.9%	2.0%	2.1%	2.1%	2.2%	2.4%	2.5%	2.7%	2.9%	3.1%	3.4%	3.6%	3.7%	3.9%	4.1%	4.2%	4.4%	4.5%	4.6%	4.7%

Figure 5.5 Estimated number of people with type 1 and type 2 diabetes in the UK between 1991 and 2013 (see Table 5.6 for data with confidence intervals)

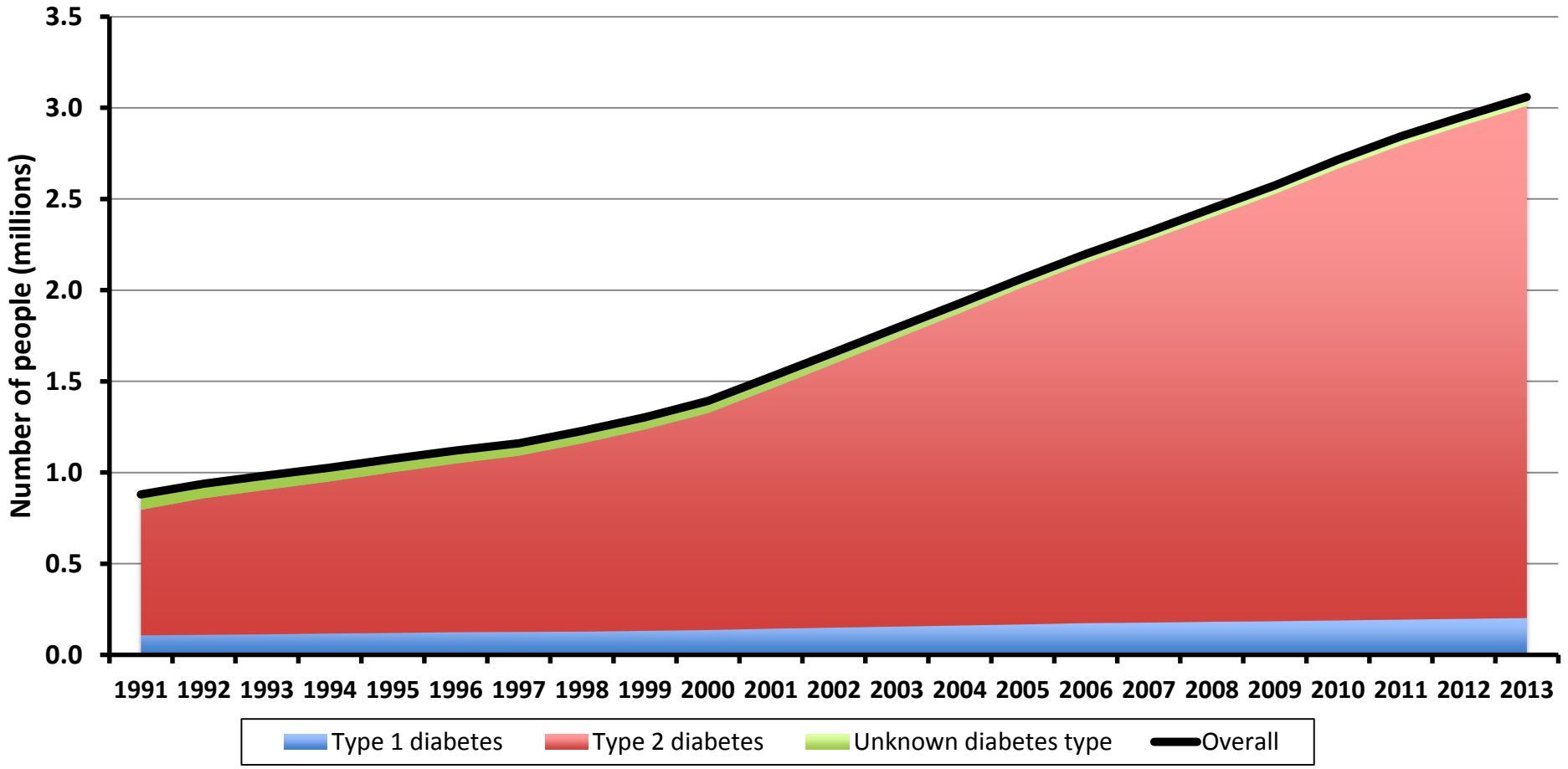


Table 5.6 Estimated number of people with type 1 and type 2 diabetes in the UK between 1991 and 2013 (data for **Figure 5.5**)

Year	Number of people with type 1 diabetes x1000 (95% CI)		Number of people with type 2 diabetes x1000 (95% CI)		Number of people with diabetes of unknown type x1000 (95% CI)		Number of people with type 1 or type 2 diabetes x1000 (95% CI)	
1991	106.3	(84.9–136.1)	689.6	(639.4–747.9)	83.9	(65.8–110.3)	879.9	(815.0–952.7)
1992	109.8	(88.9–138.3)	748.8	(698.4–806.4)	80.1	(63.2–104.5)	938.7	(875.0–1009.6)
1993	112.1	(92.0–138.7)	792.9	(744.1–848.0)	79.7	(63.7–102.2)	984.6	(923.4–1052.2)
1994	116.4	(96.6–142.2)	834.3	(786.1–888.3)	76.0	(60.9–97.1)	1026.7	(966.5–1092.7)
1995	119.2	(99.6–144.4)	882.4	(834.7–935.5)	73.7	(59.3–93.8)	1075.2	(1015.9–1140.0)
1996	123.6	(104.6–147.6)	925.1	(878.8–976.3)	71.3	(57.8–89.8)	1120.0	(1062.9–1181.9)
1997	125.3	(107.3–147.7)	966.5	(922.1–1015.0)	67.9	(55.5–84.6)	1159.6	(1105.4–1218.0)
1998	127.5	(110.3–148.5)	1031.3	(988.2–1078.1)	68.7	(56.9–84.4)	1227.6	(1175.3–1283.5)
1999	132.1	(115.8–151.6)	1103.3	(1062.2–1147.6)	67.1	(56.1–81.3)	1302.5	(1252.9–1355.2)
2000	135.8	(120.7–153.5)	1190.3	(1151.5–1231.6)	67.0	(57.0–79.6)	1393.1	(1346.7–1441.9)
2001	142.9	(127.9–160.5)	1316.3	(1276.8–1358.0)	65.1	(55.6–77.1)	1524.3	(1477.6–1573.4)
2002	148.6	(133.9–165.5)	1447.4	(1408.2–1488.8)	62.0	(53.2–73.1)	1658.1	(1611.9–1706.3)
2003	155.3	(140.5–172.2)	1580.1	(1540.1–1622.1)	58.6	(50.1–69.1)	1794.0	(1747.2–1842.7)
2004	160.6	(145.8–177.5)	1713.0	(1672.3–1755.7)	54.9	(46.9–65.0)	1928.6	(1881.3–1977.8)
2005	167.3	(152.3–184.3)	1848.1	(1806.1–1891.9)	51.5	(43.7–61.2)	2066.9	(2018.4–2117.2)
2006	173.4	(158.1–190.7)	1975.8	(1932.5–2021.1)	49.0	(41.4–58.5)	2198.2	(2148.3–2249.9)
2007	176.9	(161.5–194.3)	2095.3	(2050.8–2141.7)	48.5	(41.0–57.9)	2320.7	(2269.8–2373.5)
2008	180.8	(165.1–198.4)	2218.3	(2172.5–2266.0)	48.8	(41.3–58.3)	2447.9	(2395.6–2502.1)
2009	185.0	(169.1–202.8)	2341.6	(2294.4–2390.6)	48.8	(41.3–58.3)	2575.3	(2521.7–2630.8)
2010	188.8	(172.7–207.0)	2477.6	(2428.6–2528.4)	48.7	(41.1–58.3)	2715.1	(2659.6–2772.5)
2011	193.2	(176.6–211.8)	2601.4	(2550.7–2654.0)	49.5	(41.8–59.2)	2844.1	(2786.7–2903.3)
2012	197.5	(180.6–216.6)	2707.1	(2654.7–2761.4)	49.6	(41.8–59.4)	2954.2	(2895.1–3015.3)
2013	201.6	(184.0–221.4)	2808.3	(2753.3–2865.3)	50.3	(42.3–60.6)	3060.2	(2998.1–3124.3)

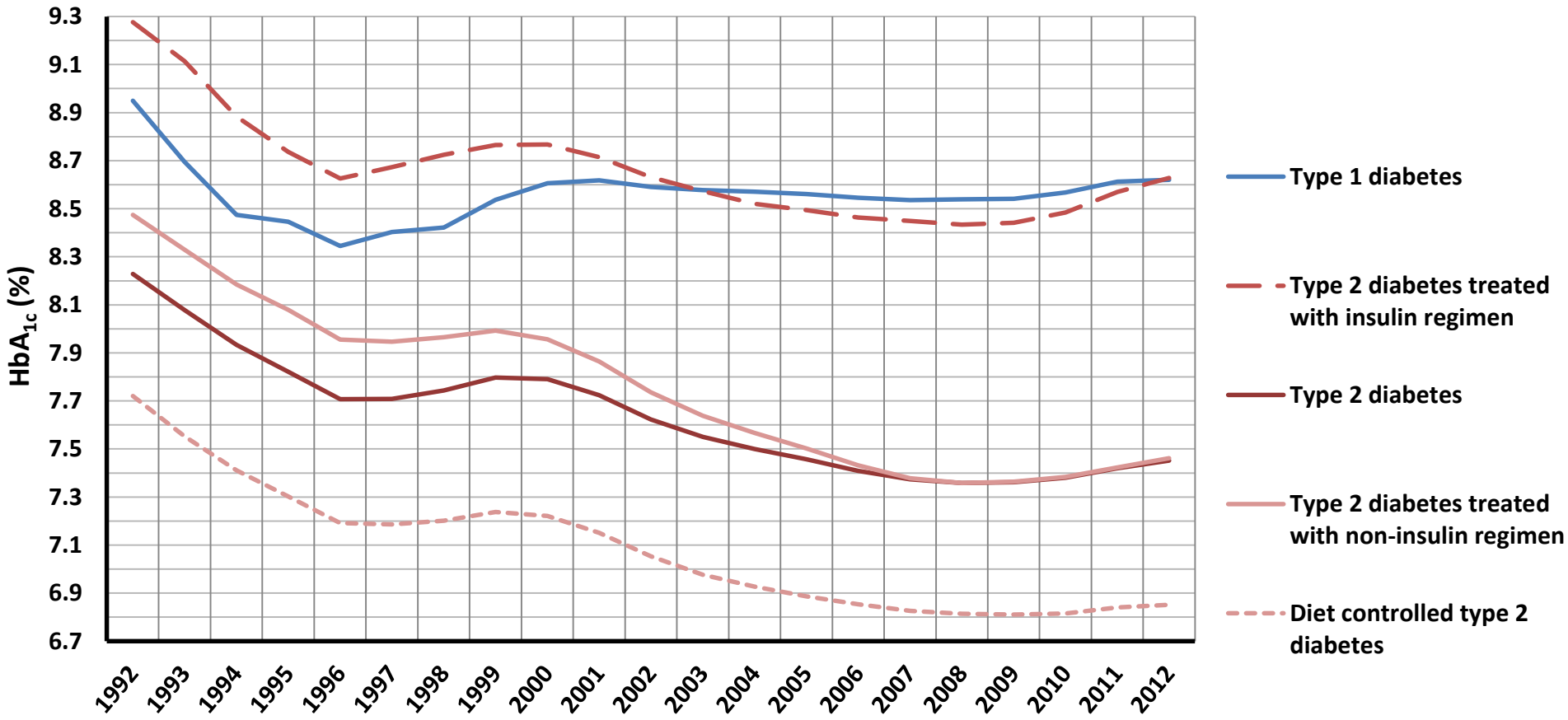
5.3.7. HbA_{1c} by year and glucose-lowering regimen in people with type 2 diabetes

For people with type 2 diabetes, HbA_{1c} decreased from 8.6% (71mmol/mol) in 1991 to 7.5% (58mmol/mol) in 2013 (where 10% and 86% of patients had a recorded HbA_{1c} level in those respective years, Figure 5.6). From 1991 onwards, HbA_{1c} was higher for people using insulin regimens than in those using non-insulin glucose lowering regimens: in 1991, this was 9.5% (80mmol/mol) versus 9.0% (75mmol/mol); in 2013, 8.7% (71mmol/mol) and 7.5% (58mmol/mol), respectively). People with type 2 diabetes controlled with diet and exercise had the lowest average HbA_{1c} for the entire study period: 8.1% (65mmol/mol) in 1991 and 6.9% (51mmol/mol) in 2013. For people with type 1 diabetes, HbA_{1c} levels decreased from 9.7% (82mmol/mol) in 1991 to 8.6% (70mmol/mol) in 2013. In these respective years, 7% and 71% of patients had a recorded HbA_{1c} value.

5.3.8. HbA_{1c} and fasting plasma glucose at diabetes presentation in people with type 2 diabetes

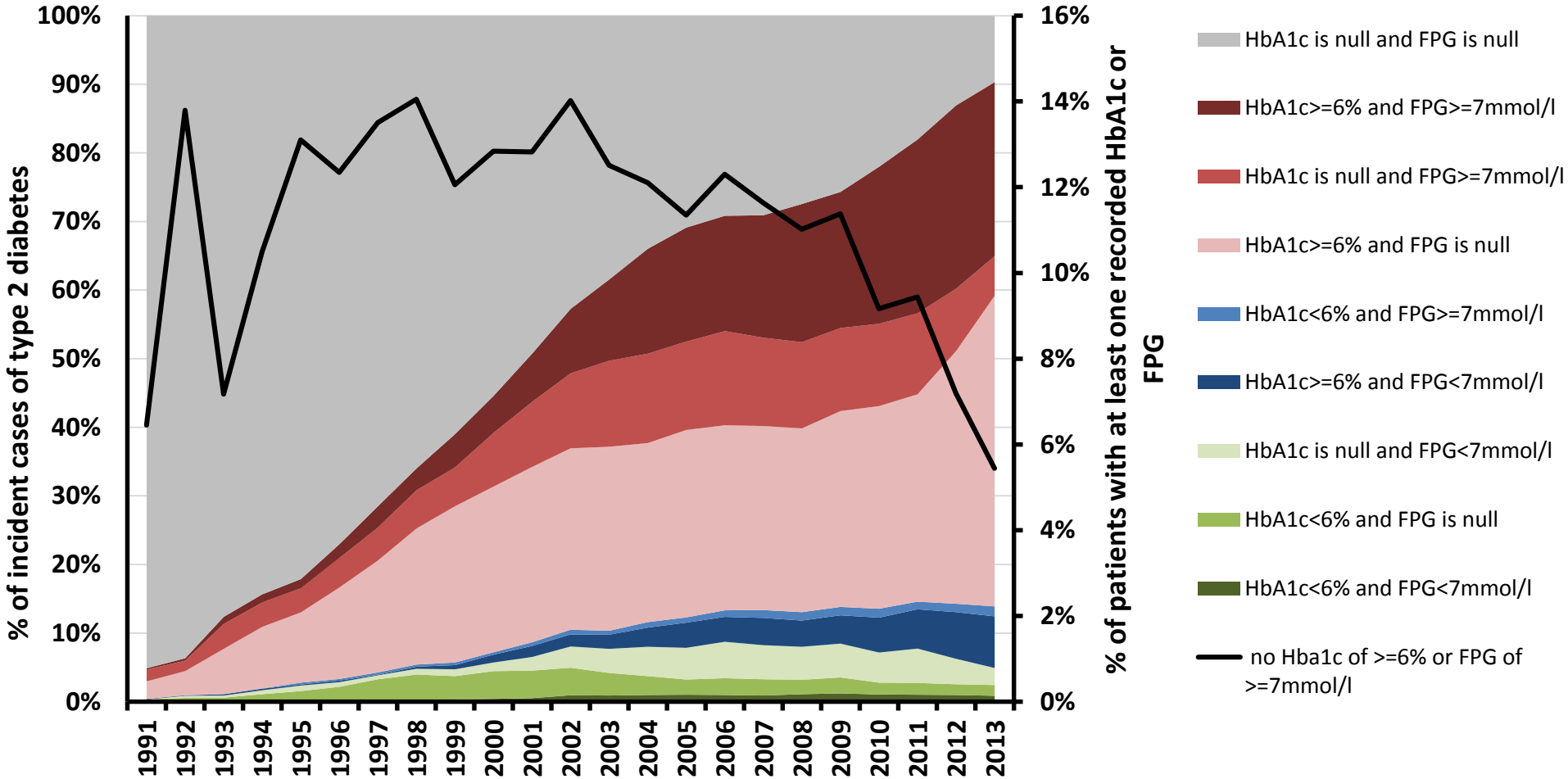
The percentage of incident cases of type 2 diabetes with no HbA_{1c} or FPG recorded at baseline decreased from 95% in 1991 to 10% in 2013 (Figure 5.7). During the same period, the percentage of incident cases with an $HbA_{1c} \geq 6\%$ (42mmol/mol) and/or FPG level ≥7mmol/l increased from 4% to 76% while the percentage of incident cases with at least one HbA_{1c} or FPG measurement at presentation but with no HbA_{1c} record ≥6% or FPG record ≥7mmol/l fluctuated from 6% in 1991 to 14% in 2002 to 5% in 2013).

Figure 5.6 HbA_{1c} by year and therapy type as a three-year rolling average



HbA_{1c} per year was defined as the nearest record within the specific year, searching in the following order: 30 days prior, 30 days after, 180 days prior and then 184 days after the index date.

Figure 5.7 HbA_{1c} and fasting plasma glucose (FPG) at time of diagnosis of type 2 diabetes



Year	HbA_{1c} <6% and FPG<7mmol/l	HbA_{1c} <6% and FPG is null	HbA_{1c} is null and FPG<7mmol/l	HbA_{1c} >=6% and FPG<7mmol/l	HbA_{1c} <6% and FPG>=7mmol/l	HbA_{1c} >=6% and FPG is null	HbA_{1c} is null and FPG>=7mmol/l	HbA_{1c} >=6% and FPG>=7mmol/l	HbA_{1c} is null and FPG is null	No HbA_{1c} of >=6% or FPG of >=7mmol/l
1991	0%	0%	0%	0%	0%	3%	2%	0%	95%	6%
1992	0%	1%	0%	0%	0%	4%	2%	0%	94%	14%
1993	0%	1%	0%	0%	0%	7%	4%	1%	88%	7%
1994	0%	1%	1%	0%	0%	9%	4%	1%	84%	10%
1995	0%	2%	1%	0%	0%	10%	3%	1%	82%	13%
1996	0%	2%	1%	0%	0%	13%	4%	2%	77%	12%
1997	0%	3%	1%	0%	0%	16%	5%	3%	72%	14%
1998	0%	4%	1%	0%	0%	20%	6%	3%	66%	14%
1999	0%	3%	1%	1%	0%	23%	6%	5%	61%	12%
2000	0%	4%	1%	1%	0%	24%	8%	5%	55%	13%
2001	1%	4%	2%	2%	1%	26%	9%	7%	49%	13%
2002	1%	4%	3%	2%	1%	26%	11%	9%	43%	14%
2003	1%	3%	4%	2%	1%	27%	13%	12%	38%	13%
2004	1%	3%	4%	3%	1%	26%	13%	15%	34%	12%
2005	1%	2%	5%	4%	1%	27%	13%	17%	31%	11%
2006	1%	2%	5%	4%	1%	27%	14%	17%	29%	12%
2007	1%	2%	5%	4%	1%	27%	13%	18%	29%	12%
2008	1%	2%	5%	4%	1%	27%	13%	20%	27%	11%
2009	1%	2%	5%	4%	1%	29%	12%	20%	26%	11%
2010	1%	2%	4%	5%	1%	30%	12%	23%	22%	9%
2011	1%	2%	5%	6%	1%	30%	12%	25%	18%	9%
2012	1%	2%	4%	7%	1%	37%	9%	27%	13%	7%
2013	1%	2%	3%	8%	1%	45%	6%	25%	10%	5%

FPG and HbA_{1c} at time of diagnosis was defined as the highest recorded value 365 days before or 30 days after the diabetes presentation data

5.3.9. Survival by year for incident diabetes cases

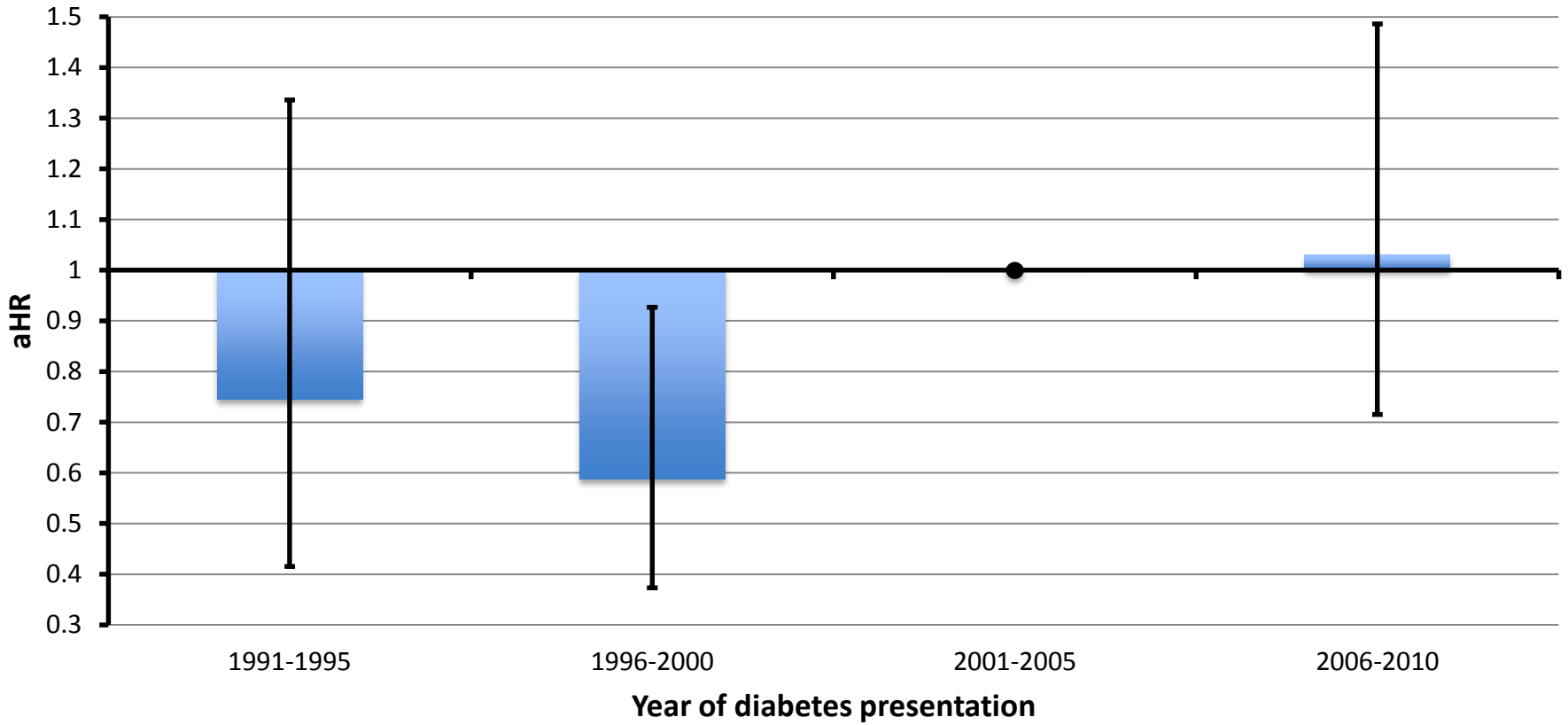
5,706 patients with type 1 diabetes and 186,921 patients with type 2 diabetes were followed up for a median of 6.3 and 4.5 years, respectively. Crude event rates for type 1 and type 2 diabetes were 8.3 and 33.7 deaths per 1,000 person-years, respectively.

For people with type 1 diabetes, increasing year of first receiving an insulin prescription was only associated with a statistically significant change in the risk of all-cause mortality for 1996–2000: aHR 0.59 (95% CI 0.37–0.93); reference years 2001–2005 (Figure 5.8). For people with type 2 diabetes, increasing year of first receiving a first prescription for a glucose-lowering medicine was associated with a decrease in the risk of mortality: aHR 1.75 (95% CI 1.60–1.92) in 1991 and 0.58 (0.48–0.70) in 2013 (reference year = 2001).

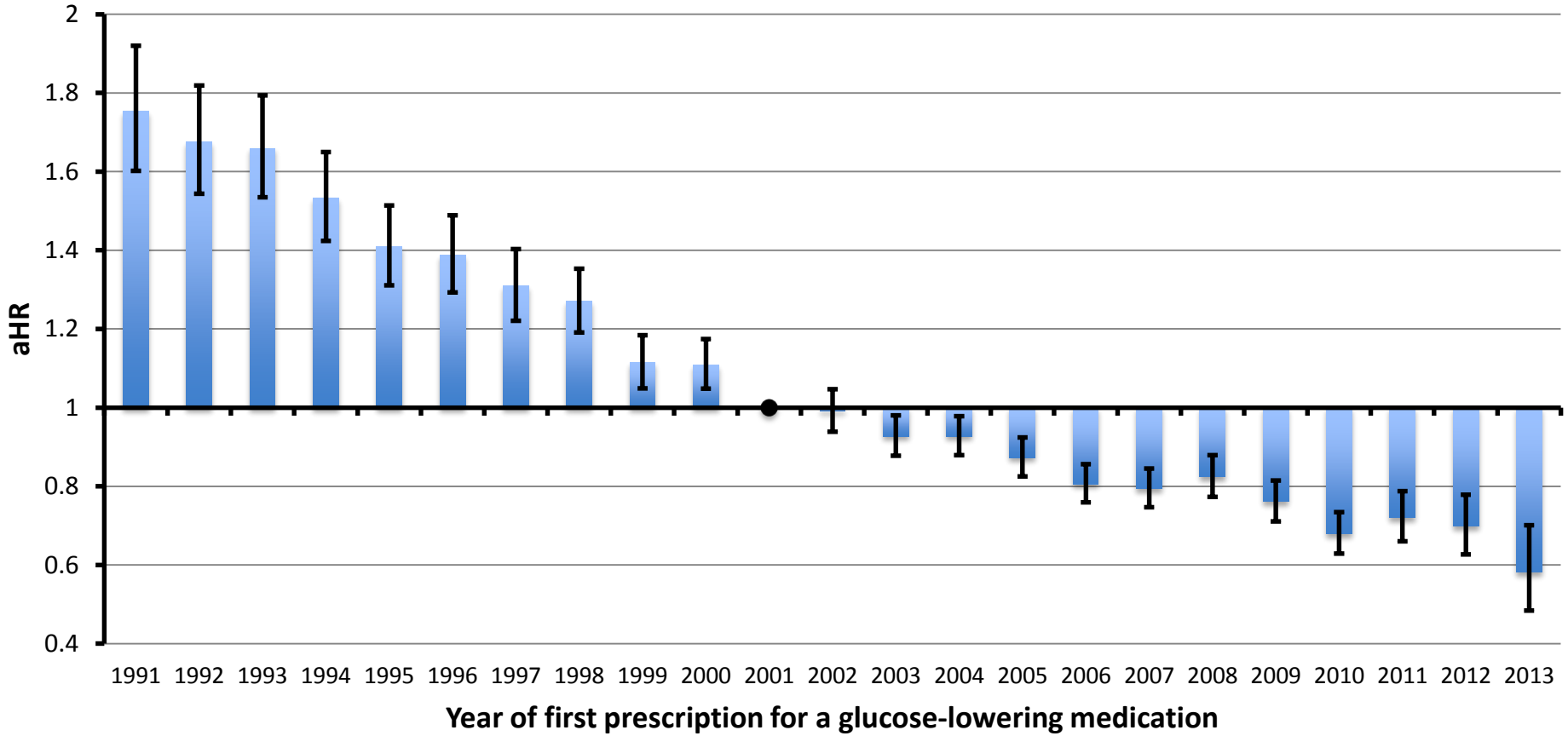
In people with type 2 diabetes, estimated median survival increased from 14 years in 1991 to 18 years in 2000 and 22 years in 2009 (Figure 5.8c).

Figure 5.8 Age- and sex-adjusted hazard ratios for all-cause mortality by year of initiating glucose-lowering therapy for type 2 diabetes

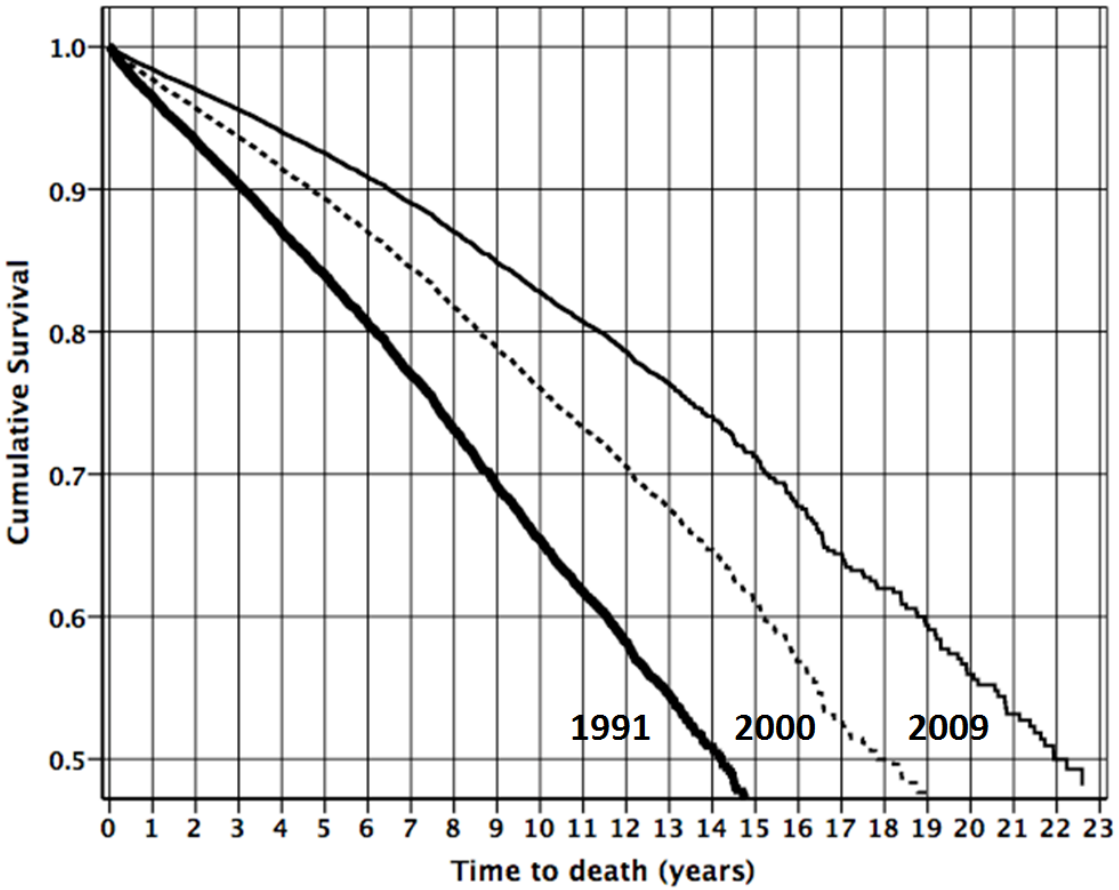
a) Adjusted hazard ratios for type 1 diabetes from the earliest of diabetes diagnosis or first prescription for insulin



b) Adjusted hazard ratios for type 2 diabetes from first glucose-lowering drug exposure



c) Estimated median survival for patients with type 2 diabetes from first glucose-lowering drug exposure



For b), the proportional hazards assumption was violated for age. Therefore age was added as a Heaviside function (<=180 days and >180 days)
For c), survival curves did not cross 0.5 for years after 2009.

5.4. Discussion

The estimated prevalence of clinically diagnosed and recorded diabetes trebled between 1991 and 2013, largely due to an increase in the prevalence of type 2 diabetes. Improvements in glucose control and survival were observed in type 2 diabetes but not in type 1 diabetes.

Diabetes UK estimated that the prevalence of diabetes was 4% in 2009, slightly lower than our estimate of 4.3%.[420] However, results from a study of diabetes prevalence in a resident population of Cardiff were similar to those estimated in this study (2.3% in 1996, increasing to 3.4% in 2005).[416] The trend of increasing prevalence of type 2 diabetes has also been observed worldwide. The latest IDF figures indicated that the worldwide prevalence of diabetes in adults is 8.3%, equating to 384 million people.[14]

5.4.1. Type 1 diabetes

5.4.1.1. Prevalence

The estimated prevalence of diagnosed and recorded type 1 diabetes increased from 0.19% (95% CI 0.18%–0.19%) in 1991 to 0.32% (95% CI 0.31%–0.32%) in 2013. The prevalence of type 1 diabetes has been estimated to have been 0.3% in 1996, and 0.4% for males and 0.3% for females in 1997.[429,430] We have previously reported an increase in the prevalence of type 1 diabetes from 0.1% in 1991 to 0.2% in 2010.[422] Here we have report a higher crude prevalence of type 1 diabetes: 0.2% in 1991, increasing to 0.3% in 2013. Possible explanations for this discrepancy include: different methods for accounting for gaps between prescriptions, differences in selection criteria, time

between diabetes diagnosis and the first prescription for insulin and time between the last prescription for insulin and the censor date.

The prevalence of type 1 diabetes calculated using data from both CPRD and HES was lower than that calculated using only CPRD data. This could indicate a regional difference in the prevalence of type 1 diabetes as all HES eligible practices were English. However, more patients in the analysis using data from both CPRD and HES were classified as diabetes of unknown type.

Increasing prevalence of type 1 diabetes could also be partly due to an increase in incidence. The World Health Organization's (WHO) Multinational Project for Childhood Diabetes (DIAMOND) found that the incidence of type 1 diabetes increased significantly worldwide between 1991 and 1999 with increases of 4.0% in Asia, 3.2% in Europe and 5.3% in North America reported [431]. In Colorado, USA, the incidence of type 1 diabetes increased 1.6-fold between 1978 and 2004 in young people aged 0–17 years [432]. The EURODIAB ACE Study Group reported an annual increase in type 1 diabetes incidence of 3.4% (95% CI 2.5%–4.4%) between 1989–1994 in Europe [433].

5.4.1.2. Glucose control

HbA_{1c} levels in people with type 1 diabetes remained relatively stable from 2000 onwards, where mean HbA_{1c} was 8.6% in 2000 and 2013. The UK's NICE recommends an HbA_{1c} target of 7.5% for glycaemic control in people with type 1 diabetes.[70] The ADA recommends an HbA_{1c} target of less than 7.5% in people below 18 years, less than 7.0% in adults and less than 7.5%–8.5% (depending upon morbidity) in older adults.[434] In the USA, 17% of young people with type 1 diabetes have been found to have poor

glycaemic control (HbA_{1c} >9.5%).[435] In Germany and Austria, HbA_{1c} in children and young adults with type 1 diabetes decreased from 8.9% in 1995 to 8.0% in 2012.[436]

The DCCT and long-term Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up study found that intensive blood-glucose control reduced the risk of microvascular and cardiovascular complications in type 1 diabetes.[216,437] In a recently published Cochrane review, the risk of developing microvascular complications was reduced for retinopathy (RR=0.27, 95% CI 0.18–0.42), nephropathy (0.56, 0.46–0.68) and neuropathy (0.35, 0.23–0.53) for intensive glycaemic control versus conventional treatment.[438] However, due to the small number of events, no firm conclusion could be reached regarding macrovascular outcomes.[438] In a recent paper from the EURODIAB cohort, a U-shaped association was reported between HbA_{1c} and all-cause mortality, with the lowest risk being reported for patients with an HbA_{1c} of 7–8%.[439] Other studies have reported an association between worsening glycaemic control and increased risk of cardiovascular disease and cardiovascular and all-cause mortality.[440–442] Even people with good glycaemic control (HbA_{1c} ≤6.9%) had double the risk of death when compared with people without diabetes.[442]

5.4.1.3. Relative survival

There was no reduction in all-cause mortality in those with type 1 diabetes during the study period. However, the length of follow-up from disease incidence was relatively short (mean 7.0, median 6.3 years). Therefore, our estimates are likely to relate to short-term mortality in type 1 diabetes rather than mortality due to diabetic complications such as cardiovascular disease. A study using data from 13 population-based EURODIAB registers found that there was significant excess mortality in people

with type 1 diabetes diagnosed in childhood in the absence of late diabetic complications.[443] One-third of deaths were directly attributed to diabetes and many of these deaths mentioned ketoacidosis.[443] Duration of type 1 diabetes has been shown to be associated with a higher adjusted mean rate of cardiovascular disease (4% for durations of 21–40 years versus 0.8% for 1–20 years).[441]

Several studies have reported a reduction in the risk of all-cause and cardiovascular mortality[66,444–446] and a corresponding increase in life expectancy over time in people with type 1 diabetes.[447] However, one study reported that mortality rates for people with type 1 diabetes only decreased between 1968 and 1984, before reaching a plateau between 1984 and 1998.[448] People with type 1 diabetes diagnosed between the ages of 0–14 had improved survival in 1970–1974 compared with 1985–1989.[449] However, the reverse was true for people diagnosed between the ages of 15–29.[449] Nephropathy was found to be the biggest factor in the excess mortality seen in type 1 diabetes.[445,450] Amputation and poor visual acuity have also been reported to be significant predictors of mortality in people with type 1 diabetes.[451]

5.4.2. Type 2 diabetes

5.4.2.1. Prevalence

We have previously demonstrated that the incidence of diagnosed and recorded type 2 diabetes increased three-fold in the UK between 1991 and 2010 and that the percentage of people diagnosed before the age of 40 years increased with each increasing five-year calendar period (5.9% for 1991–1995 and 12.4% for 2006–2010).[421] Previous studies have estimated that the prevalence of type 2 diabetes was 1.2% in 1996[429] and 2.0% for males and 1.7% for females in 1997 (in Clwyd, Wales).[430]

Masso González and colleagues reported an increase in prevalence of type 2 diabetes from 2.6% to 4.3% between 1996 and 2005.[9]

The increase in type 2 diabetes prevalence is linked to obesity. Between 1993 and 2010, the proportion of obese people increased from 13% to 26% for men and from 16% to 26% for women.[13] The age of onset of type 2 diabetes has been shown to be inversely related to BMI,[22] and intensive lifestyle intervention with a minimum of 7% weight loss and 150 minutes of physical activity per week has been shown to reduce the incidence rate for diabetes by 58%.[23]

The increase in the prevalence of type 2 diabetes may also be due to increasing diabetes ascertainment. As the early symptoms of type 2 diabetes can be mild, people with type 2 diabetes can remain undiagnosed for many years.[17] Improved detection of type 2 diabetes through, for example, the implementation in the UK of the National Diabetes Framework, NHS Health Checks and QOF, may have led to earlier diagnosis of type 2 diabetes. In addition, changes were made to the criteria for diagnosing type 2 diabetes during the study period, including the introduction of the WHO's new diagnostic criteria.[405] Here we found evidence that there has been misclassification of type 2 diabetes, and of a magnitude that was surprisingly high. Furthermore, as the longevity of the UK population increases, more people live long enough to develop type 2 diabetes.[452] In addition, improvements in diabetes management have also increased life expectancy for people with diabetes.[152,452–456] Improved recording of diabetes diagnoses may have occurred during the study period.

5.4.2.2. Glucose control

NICE and EASD/ADA guidelines recommend HbA_{1c} targets of 6.5% and 7%, respectively, although a target of 7.5% may be necessary for some people.[7,55] HbA_{1c} levels remained higher than NICE recommendations for those people with type 2 diabetes treated with insulin regimens during the study period. Other observational studies have also shown that patients with type 2 diabetes have poor control and delayed treatment intensification.[457–461]

The UKPDS found that intensive control of blood glucose reduced the risk of developing microvascular but not macrovascular complications.[67] However, after the 10-year follow-up observational study, cardiovascular benefits associated with intensive control were reported.[112] Subsequent randomised controlled trials and meta-analyses have not demonstrated that intensive treatment was associated with a significantly reduced risk of cardiovascular events[79,217,218] or mortality.[111] Observational studies have reported a U-shaped association between HbA_{1c} levels and an increased risk of all-cause mortality and cardiac events.[60,222–224]

5.4.2.3. Relative survival

Reduced risk of all-cause mortality in people with type 2 diabetes suggests that the overall management of this condition has improved. In people with type 2 diabetes, estimated median survival increased from 14 years in 1991 to 22 years in 2009. To put this in context, for 63 years olds (the mean age of subjects in this analysis), overall life expectancy increased from 15.3 years in 1991 to 19.1 years in 2009 for males and from 19.3 years to 21.9 years, respectively, for females.[462] However, this is not a direct comparison as mean and median survival has been compared. During the study period,

reductions in systolic blood pressure and total cholesterol were observed for people with type 2 and type 1 diabetes, whilst the number of people receiving antihypertensive, lipid-lowering and antiplatelet therapy increased. Life expectancy in type 2 diabetes has been shown to vary depending on several risk factors, including HbA_{1c}, blood pressure, the ratio of total:HDL cholesterol and diabetes duration.[161] The launch of novel glucose-lowering medications,[69] diabetes teaching programmes, improved detection of diabetic complications and tobacco reforms may have also contributed to improved survival during the study period. Numerous studies have reported a reduced risk of all-cause and cardiovascular disease mortality in people with diabetes,[152–159] and with type 2 diabetes specifically.[66] However, one study has reported that improvement in survival of people with diabetes between 1971–1986 and 1988–2000 was limited to men.[463] A US population study found that the mortality burden associated with diabetes mellitus increased significantly from 1970–1994.[160] However, earlier diagnosis of type 2 diabetes through improved detection and changes in diagnostic criteria may cause an apparent improvement in survival following diabetes diagnosis, even in the absence of a genuine improvement in survival following true diabetes onset. The contribution of earlier diagnosis to the overall improvement in survival observed during the study period cannot be quantified.

5.4.3. Study limitations

CPRD GOLD is a very large longitudinal dataset which has been shown to be representative of the population in terms of crude mortality and the age and gender structure.[364,365] However, age-standardised mortality rates are 9–13% lower than the national average.[364] In a systematic review, a positive predictive value of more than

50% was reported for most conditions investigated.[367] Patient consulting rates for diabetes were reported to be lower in GPRD when compared with those obtained from the 4th National Study of Morbidity Statistics from General Practice (MSGP4) in a study conducted between September 1991 and August 1992.[464] However, data recording practices differed between sources.[464] Chronic conditions may only be recorded at diagnosis in GPRD whereas every consultation was recorded in MSGP4.[464] In a more recently conducted systematic review, Herrett and colleagues, reported that the median proportion of cases with a confirmed diagnosis was 89% (range 24–100%).[368] and these data are generally representative of the UK population. However, misclassification of diabetes type was possible due to the recording of conflicting diagnoses or the absence of a record for a specific diabetes type. Changes to the coding of diabetes may have occurred in recent years. 'Insulin-dependent diabetes mellitus' or IDDM was commonly used in earlier years, and some people with type 2 diabetes receiving prescriptions for insulin may have been attributed a code for IDDM leading to misclassification. HbA_{1c} or glucose levels were not used in the selection criteria. However, a series of decision rules was applied to maintain consistency in patient selection (Table 5.1).

The true prevalence of diabetes cannot be calculated from CPRD, as the number of people with undiagnosed diabetes cannot be determined, although improved detection of diabetes may have led to better diagnosis of type 2 diabetes in more recent years. The symptoms of type 2 diabetes can be mild, and people with the condition may remain undiagnosed initially. Conversely, severe symptoms develop quickly after the onset of type 1 diabetes. This condition is therefore normally diagnosed and treated quickly.

5.4.4. Conclusion

The estimated prevalence of diagnosed and recorded type 2 diabetes increased markedly and consistently in the UK over the two decades between 1991 and 2013. Improvements in glucose control and survival were observed in people with type 2 diabetes but not in people with type 1 diabetes. However, the short follow-up time needs to be taken into account when interpreting survival in type 1 diabetes. In addition to higher incidence, improved survival in people with type 2 diabetes explains, in part, the increased prevalence rates observed between 1991 and 2013.

6. Prevalence of insulin use and an estimate of the number of insulin users in the UK between 1991 and 2010

This is the accepted version of the following article: Holden SE, Gale EA, Jenkins-Jones S, Currie CJ. How many people inject insulin? UK estimates from 1991 to 2010. *Diabetes Obes Metab* 2014:16:553-9. This study has been published in final form at [http://onlinelibrary.wiley.com/doi/10.1111/dom.12260/abstract]. Deviations from the published version of this manuscript are underlined. The discussion is based on the accepted version of the manuscript published by Diabetes Obesity and Metabolism and the submitted and pre-peer reviewed drafts of the manuscript.

6.1. Introduction

6.1.1. Background

In the UK, the overall prevalence of diabetes increased from 2.8% to 4.3% between 1996 and 2005. This has been largely driven by an increase in the prevalence of type 2 diabetes.[9] In terms of the UK population as a whole, the estimated number of people with diabetes has risen from 1.4 million to 2.8 million between 1996 and 2010.[420] The management of patients with diabetes involves the lowering of blood glucose and the control of cardiovascular risk factors. Type 1 diabetes results from the autoimmune destruction of insulin producing beta cells in the pancreas and therefore the use of exogenous insulin is essential in these patients. However, type 2 diabetes is a progressive condition characterised by insulin resistance and relative insulin insufficiency and can be managed by one or a combination of lifestyle factors, oral glucose-lowering medication, non-insulin injectable glucose-lowering medication and

insulin. NICE generally recommends insulin as third line therapy in type 2 diabetes when metformin and a sulfonylurea, where tolerated have not adequately controlled HbA_{1c} levels.[55]

UKPDS reported that improved glucose control through the earlier use of glucose-lowering therapies (insulin and sulfonylureas) reduced the risk of microvascular but not macrovascular complications, all-cause mortality or quality of life.[67] In addition, the UKPDS demonstrated that the use of metformin was associated with a reduced risk of diabetes-related endpoints. Subsequently, metformin has been recommended as first line therapy for many people with type 2 diabetes.[82] UKPDS may have also influenced clinical practice as lower targets were advocated for blood glucose control. This may have encouraged the early elective use of insulin.

Currently, there are no estimates of the number of people with type 1 and type 2 diabetes using insulin in the UK. However, the number of items and overall volume of insulin dispensed has increased year on year (Chapter 7). Between 2000 and 2009, the total annual cost of insulin in the UK increased from £156 million in 2000 to £359 million in 2009 (adjusted to 2010 prices) (Chapter 7). This is, at least in part, due to the introduction of more expensive insulin analogues and the more frequent use of insulin in type 2 diabetes. In England alone, the total cost of medicines used to treat diabetes increased from £573.9 million to £725.1 million between 2005/6 and 2009/10 and the cost of insulin prescriptions increased from £220.8 million to £307.5 million during the same period.[465] In the US, 25.8 million people (8.3% of the population) had diabetes in 2010[466] and the number of people treated with insulin increased from 3.4 million (33.4%) in 1997 to 5.7 million (27.5%) in 2010. However, this represented a decrease in the proportion of people with diabetes using insulin in people over 40.[467–469]

6.1.2. Aims and objectives

The aim of this study was to calculate the rates of insulin and the relative rates of insulin use in type 1 and type 2 diabetes in the UK population.

6.2. Methods

6.2.1. CPRD

The data source used for this study was CPRD. CPRD contains clinically rich, pseudonymized data collected in a non-interventional manner from the daily record keeping of primary care physicians in the UK. These data include patient demographics and registration information, consultations, medical history and diagnoses, test results, immunizations, referrals, outpatient letters and prescriptions. CPRD is broadly representative of the UK population and contains to date over 12 million research-quality patients registered at 660 practices. The data extract used in this study included records up to June 2012.

6.2.2. Prevalence of insulin use in the UK

In this retrospective study, patients denoted by CPRD as being of research quality were identified if they had received a prescription for insulin within the study period (1991 to 2010). The index date was the date of a patient's first prescription for insulin. Patients were classed as a prevalent case until the date of their last insulin prescription or the date of their transferring out of practice or the end of the study period, whichever was earliest. Patients using insulin were assigned a diagnosis of type 1 or type 2 diabetes using a series of decision rules based on age at diagnosis, diagnosis type (type 1, type 2, or type unspecified), and history of prescriptions for insulin and other glucose-lowering medicines (Table 6.1). Patients were assigned a diagnosis of secondary diabetes if they had a code suggestive of secondary diabetes in their CPRD record. A small number of patients who had unclassifiable diabetes type were assigned

to type 1 or type 2 depending on the ratio of patients with type 1 to type 2 diabetes amongst known cases stratified by age (five-year groups) and sex.

Table 6.1 Decision rules implemented to assign a diagnosis of type 1 or type 2 diabetes to the insulin users.

Type 1 diagnosis	Type 2 diagnosis	Diagnosis of unknown diabetes type	Insulin Rx	OHA prescription	More than one OHA	Age at presentation	Diabetes type	Extra criteria
1	1	1	1	1	1	<35	2	
1	1	1	1	1	1	>=35	2	
1	1	1	1	1	0	<35	2	
1	1	1	1	1	0	>=35	2	
1	1	1	1	0	0	<35	1	
1	1	1	1	0	0	>=35	2	12-month wash-in
1	1	0	1	1	1	<35	2	
1	1	0	1	1	1	>=35	2	
1	1	0	1	1	0	<35	2	
1	1	0	1	1	0	>=35	2	
1	1	0	1	0	0	<35	1	
1	1	0	1	0	0	>=35	2	12-month wash-in
1	0	1	1	1	1	<35	2	
1	0	1	1	1	1	>=35	2	
1	0	1	1	1	0	<35	1	If OHA<1yr
1	0	1	1	1	0	>=35	x	
1	0	1	1	0	0	<35	1	
1	0	1	1	0	0	>=35	1	
1	0	0	1	1	1	<35	2	
1	0	0	1	1	1	>=35	2	
1	0	0	1	1	0	<35	1	If OHA<1yr
1	0	0	1	1	0	>=35	x	
1	0	0	1	0	0	<35	1	

Type 1 diagnosis	Type 2 diagnosis	Diagnosis of unknown diabetes type	Insulin Rx	OHA prescription	More than one OHA	Age at presentation	Diabetes type	Extra criteria
1	0	0	1	0	0	>=35	1	
0	1	1	1	1	1	<35	2	
0	1	1	1	1	1	>=35	2	
0	1	1	1	1	0	<35	2	
0	1	1	1	1	0	>=35	2	
0	1	1	1	0	0	<35	2	
0	1	1	1	0	0	>=35	2	12-month wash-in
0	1	0	1	1	1	<35	2	
0	1	0	1	1	1	>=35	2	
0	1	0	1	1	0	<35	2	
0	1	0	1	1	0	>=35	2	
0	1	0	1	0	0	<35	2	
0	1	0	1	0	0	>=35	2	12-month wash-in
0	0	1	1	1	1	<35	2	
0	0	1	1	1	1	>=35	2	
0	0	1	1	1	0	<35	1	If OHA<1yr
0	0	1	1	1	0	>=35	2	12-month wash-in
0	0	1	1	0	0	<35	1	
0	0	1	1	0	0	>=35	2	12-month wash-in
0	0	0	1	1	1	<35	2	
0	0	0	1	1	1	>=35	2	
0	0	0	1	1	0	<35	1	If OHA<1yr
0	0	0	1	1	0	>=35	2	12-month wash-in
0	0	0	1	0	0	<35	1	
0	0	0	1	0	0	>=35	x	

The method used to calculate the point prevalence of insulin use was similar to that of a census. If a patient was using insulin at the mid-year point they were included as a prevalent case regardless of their duration of therapy. However, in order to be included, the patient had to have a prescription for insulin issued on or before 30th June of the year in question and a prescription issued on or after 30th June of the same year. Although theoretically a patient could have been included as a prevalent case if they had only received one prescription for insulin provided it was issued on exactly the 30th June, the majority of patients included will have received at least two prescriptions for insulin before and after the mid-year point. The prevalence of insulin use was then calculated by dividing the number of insulin users in CPRD on the 30th June each year from 1991 to 2010 by the number of patients in CPRD on the same date. The prevalence of type 1 and type 2 diabetes was calculated using the same formula. The age- and sex-stratified prevalence of insulin use per diabetes type was then multiplied by the total UK population from data from the ONS[428] to produce an estimate of the number of insulin users in the UK.

Treatment patterns per year were determined for prevalent cases of type 2 diabetes treated with insulin. The percentage of patients with type 2 diabetes using insulin was then calculated by dividing the number of patients with type 2 diabetes using insulin by the total number of patients with type 2 diabetes (i.e. those patients with type 2 diabetes using insulin or other glucose-lowering medicines or being diet-controlled) at the mid-year point. Diet-controlled patients were identified if they had type 2 diabetes but had received no prescriptions for a glucose-lowering medication prior to the mid-year point (relaxed criteria). As a sensitivity analysis, we also applied more strict selection criteria for diet-controlled diabetes where at least one of the following

criteria must also apply: more than one prescription for a glucose biosensor strip or a Read code for diabetes on diet only.

6.2.3. Incident cases of insulin use

Baseline characteristics were generated only for incident cases of insulin use. Incident cases were identified as patients who had received their first prescription for insulin within the study period and had a wash-in period of at least 365 days between their registration date and their first insulin prescription.

6.2.4. Statistical analysis

Wilson (or score) 95% confidence intervals were calculated for prevalence rates,[385] and the linear-by-linear Chi-square test was used to test if there was any association between calendar year and the number of insulin users in CPRD. All statistical analysis was carried out in SPSS PASW Statistics 18.

6.3. Results

6.3.1. Baseline characteristics

The overall mean age at insulin initiation increased with each increasing five-year period from 52.5 years (SD 20.5) in 1991–1995 to 58.1 (19.9) in 2005–2010 (Table 6.2). Between 1991–1995 and 2006–2010, the baseline mean (SD) HbA_{1c} at insulin initiation was 10.0% (2.6%) in 1991–1995, 9.7% (2.0%) in 1996–2000, 9.7% (1.9%) in 2001–2005, and 9.8% (2.0%) in 2006–2010. The baseline characteristics for incident cases of insulin use are detailed in Table 6.2.

6.3.2. CPRD: total users and prevalence of insulin treatment

The number of insulin users at the mid-year point in CPRD increased from 8,065 in 1991 to 42,518 in 2010 (Table 6.3). During the same period, the number of people in CPRD increased from 3.32 million to 6.34 million. The crude prevalence of insulin use increased from 1.74 (95% CI 1.69–1.78) and 0.67 (0.64–0.70) per 1,000 people in 1991, to 2.23 (2.20–2.27) and 4.38 (4.32–4.43) per 1,000 in 2009, before decreasing to 2.21 (2.18–2.25) and 4.34 (4.29–4.39) per 1,000 people in 2010, for patients with type 1 ($P<0.001$) and type 2 ($P<0.001$) diabetes, respectively. The overall crude prevalence of insulin use increased from 2.43 (2.38–2.49) per 1,000 people in 1991 to 6.76 (6.70–6.83) per 1,000 people in 2009, before decreasing to 6.71 (6.64–6.77) per 1,000 people in 2010 ($P<0.001$).

Table 6.2 Baseline characteristics in CPRD for incident cases of insulin use

Parameter	1991–1995	1996–2000	2001–2005	2006–2010
n	6,033	13,386	19,557	17,037
Male, n (%)	3,126 (51.8)	7,047 (52.6)	11,021 (56.4)	10,008 (58.7)
Age at first insulin Rx, years				
Mean (SD)	52.5 (20.5)	56.3 (19.5)	58.0 (19.1)	58.1 (19.9)
Median (IQR)	57.0 (38.0–68.0)	61.0 (46.0–70.0)	62.0 (49.0–72.0)	62.0 (49.0–72.0)
Smoking, n (%)				
Non-	3,441 (57.0)	7,123 (53.2)	8,619 (44.1)	6,174 (36.2)
Ex-	656 (10.9)	2,637 (19.7)	6,565 (33.6)	7,242 (42.5)
Current	1,236 (20.5)	2,860 (21.4)	3,856 (19.7)	3,008 (17.7)
Unknown	700 (11.6)	766 (5.7)	517 (2.6)	613 (3.6)
HbA_{1c} (%)				
n (%)	841 (14)	5,349 (40)	14,382 (74)	14,187 (83)
Mean (SD), %	10.0 (2.6)	9.7 (2.0)	9.7 (1.9)	9.8 (2.0)
Mean (SD), mmol/mol	85.4 (27.9)	83.0 (21.8)	82.0 (21.2)	83.8 (22.4)

Table 6.3 Number and prevalence of insulin use in CPRD

Year	Number of cases CPRD				Number of people in CPRD	Prevalence per 1,000 population (95% CI)			
	Type 1 diabetes	Type 2 diabetes	Secondary diabetes	Total		Type 1 diabetes	Type 2 diabetes	Secondary diabetes	Total
1991	5,767	2,227	71	8,065	3,316,316	1.74 (1.69–1.78)	0.67 (0.64–0.70)	0.02 (0.02–0.03)	2.43 (2.38–2.49)
1992	6,316	2,824	100	9,240	3,569,712	1.77 (1.73–1.81)	0.79 (0.76–0.82)	0.03 (0.02–0.03)	2.59 (2.54–2.64)
1993	6,838	3,472	122	10,432	3,838,099	1.78 (1.74–1.82)	0.90 (0.88–0.94)	0.03 (0.03–0.04)	2.72 (2.67–2.77)
1994	7,317	4,228	142	11,687	4,122,398	1.77 (1.73–1.82)	1.03 (1.00–1.06)	0.03 (0.03–0.04)	2.84 (2.78–2.89)
1995	7,590	4,962	169	12,721	4,381,006	1.73 (1.69–1.77)	1.13 (1.10–1.16)	0.04 (0.03–0.04)	2.90 (2.85–2.95)
1996	8,142	5,867	203	14,212	4,638,588	1.76 (1.72–1.79)	1.26 (1.23–1.30)	0.04 (0.04–0.05)	3.06 (3.01–3.11)
1997	8,907	7,204	247	16,358	4,861,244	1.83 (1.79–1.87)	1.48 (1.45–1.52)	0.05 (0.04–0.06)	3.36 (3.31–3.42)
1998	9,529	8,560	297	18,386	5,044,775	1.89 (1.85–1.93)	1.70 (1.66–1.73)	0.06 (0.05–0.07)	3.64 (3.59–3.70)
1999	10,079	10,514	350	20,943	5,218,564	1.93 (1.89–1.97)	2.01 (1.98–2.05)	0.07 (0.06–0.07)	4.01 (3.96–4.07)
2000	10,743	12,995	420	24,158	5,395,114	1.99 (1.95–2.03)	2.41 (2.37–2.45)	0.08 (0.07–0.09)	4.48 (4.42–4.53)
2001	11,301	15,203	469	26,973	5,539,020	2.04 (2.00–2.08)	2.74 (2.70–2.79)	0.08 (0.08–0.09)	4.87 (4.81–4.93)
2002	11,868	17,376	552	29,796	5,664,016	2.10 (2.06–2.13)	3.07 (3.02–3.11)	0.10 (0.09–0.11)	5.26 (5.20–5.32)
2003	12,474	19,633	615	32,722	5,796,955	2.15 (2.11–2.19)	3.39 (3.34–3.43)	0.11 (0.10–0.11)	5.64 (5.58–5.71)
2004	12,969	22,087	706	35,762	5,939,605	2.18 (2.15–2.22)	3.72 (3.67–3.77)	0.12 (0.11–0.13)	6.02 (5.96–6.08)
2005	13,699	24,307	796	38,802	6,103,500	2.24 (2.21–2.28)	3.98 (3.93–4.03)	0.13 (0.12–0.14)	6.36 (6.29–6.42)
2006	13,944	25,681	865	40,490	6,191,800	2.25 (2.21–2.29)	4.15 (4.10–4.20)	0.14 (0.13–0.15)	6.54 (6.48–6.60)
2007	14,068	26,658	923	41,649	6,276,979	2.24 (2.20–2.28)	4.25 (4.20–4.30)	0.15 (0.14–0.16)	6.64 (6.57–6.70)
2008	14,227	27,622	962	42,811	6,334,429	2.25 (2.21–2.28)	4.36 (4.31–4.41)	0.15 (0.14–0.16)	6.76 (6.69–6.82)
2009	14,259	27,922	986	43,167	6,382,181	2.23 (2.20–2.27)	4.38 (4.32–4.43)	0.15 (0.15–0.16)	6.76 (6.70–6.83)
2010	14,017	27,530	971	42,518	6,338,431	2.21 (2.18–2.25)	4.34 (4.29–4.39)	0.15 (0.14–0.16)	6.71 (6.64–6.77)

6.3.3. Estimates of UK insulin users

The estimated number of insulin users in the UK increased from 136,800 (95% CI 120,700–155,200) in 1991 to 421,300 (399,800–444,100) in 2010 (Table 6.4). In 1991, more people using insulin had type 1 diabetes than had type 2 diabetes (98,400 [85,000–114,300] versus 37,000 [30,200–46,200]). By 2010, this situation had reversed, where 134,900 (123,100–148,000) and 277,400 (262,800–293,300) had type 1 and type 2 diabetes, respectively (Table 6.4).

6.3.4. Insulin use in type 2 diabetes

The prevalence rate of people with type 2 diabetes injecting insulin increased from 0.67 (0.64–0.70) per 1,000 people in 1991 to 4.34 (4.29–4.39) per 1,000 people in 2010: a 6.5-fold increase (Table 6.3). The total number of people with type 2 diabetes injecting insulin increased from 37,000 (30,200–460,200) in 1991 to 277,400 (262,800–293,300) in 2010: a 7.5-fold increase (Table 6.4).

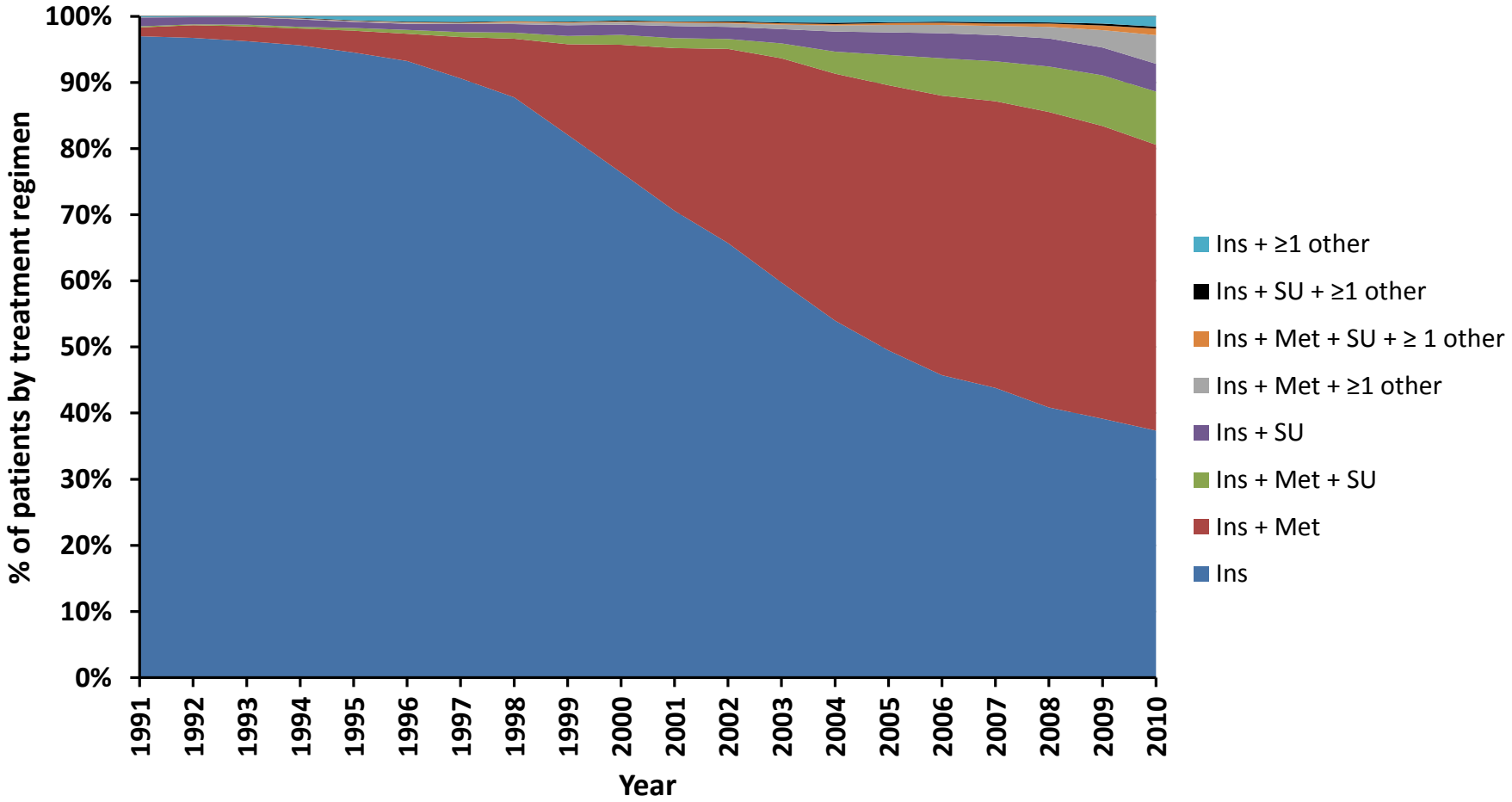
Taking prevalent cases of insulin use for patients with type 2 diabetes, the majority of patients in 1991 were treated with insulin alone (97%; Figure 6.1), with the largest percentage of patients receiving premixed insulin (52%). By 2010, more patients were treated with a combination of insulin plus at least one type of oral glucose-lowering medication (63%) than with insulin alone (37%), with the largest percentage of patients (43%) receiving a combination of premixed insulin plus metformin.

Table 6.4 Estimated number of insulin users in the UK

	Estimated number of insulin users x1,000 (95% CI)			
Year	Type 1 diabetes	Type 2 diabetes	Secondary diabetes	Total
1991	98.4 (85.0–114.3)	37.0 (30.2–46.2)	1.3 (0.6–4.5)	136.8 (120.7–155.2)
1992	100.5 (87.4–115.8)	43.8 (36.6–53.3)	1.7 (0.8–4.9)	146.0 (130.0–164.3)
1993	101.3 (88.6–116.2)	50.5 (43.0–60.2)	1.9 (1.0–5.0)	153.8 (137.8–171.9)
1994	101.0 (88.8–115.3)	57.8 (50.0–67.6)	2.1 (1.1–5.0)	161.0 (145.1–178.7)
1995	98.9 (87.1–112.6)	64.3 (56.3–74.2)	2.3 (1.2–5.2)	165.5 (149.9–183.0)
1996	100.4 (88.8–113.7)	72.4 (64.0–82.4)	2.6 (1.5–5.5)	175.3 (159.6–192.7)
1997	105.0 (93.4–118.3)	85.6 (76.7–96.1)	2.9 (1.7–5.8)	193.5 (177.3–211.4)
1998	108.5 (96.9–121.7)	98.8 (89.4–109.9)	3.4 (2.0–6.3)	210.7 (194.1–228.9)
1999	111.3 (99.7–124.4)	118.4 (108.3–130.2)	3.9 (2.4–6.9)	233.6 (216.4–252.3)
2000	115.2 (103.6–128.3)	142.9 (131.9–155.5)	4.5 (2.9–7.6)	262.6 (244.6–282.1)
2001	118.6 (107.0–131.7)	164.1 (152.3–177.3)	4.9 (3.2–8.1)	287.6 (268.9–307.7)
2002	122.2 (110.5–135.3)	184.1 (171.8–197.9)	5.6 (3.8–8.9)	311.9 (292.7–332.6)
2003	125.7 (114.0–138.7)	204.9 (192.0–219.2)	6.1 (4.2–9.5)	336.7 (316.9–357.8)
2004	128.1 (116.4–141.2)	226.4 (213.0–241.2)	6.9 (4.8–10.3)	361.4 (341.1–383.0)
2005	132.5 (120.7–145.6)	244.9 (231.1–260.1)	7.6 (5.4–11.1)	385.0 (364.3–407.0)
2006	133.7 (122.0–146.8)	256.2 (242.2–271.6)	8.1 (5.9–11.7)	398.1 (377.2–420.4)
2007	133.9 (122.2–146.9)	264.4 (250.1–279.9)	8.6 (6.3–12.2)	406.8 (385.7–429.2)

Year	Type 1 diabetes	Type 2 diabetes	Secondary diabetes	Total
2008	135.0 (123.4–148.0)	273.6 (259.1–289.3)	8.9 (6.6–12.5)	417.4 (396.2–440.0)
2009	135.1 (123.4–148.2)	276.7 (262.2–292.6)	9.1 (6.7–12.8)	420.9 (399.6–443.6)
2010	134.9 (123.1–148.0)	277.4 (262.8–293.3)	9.1 (6.7–12.8)	421.3 (399.8–444.1)

Figure 6.1 Treatment patterns for prevalent cases of insulin use with type 2 diabetes



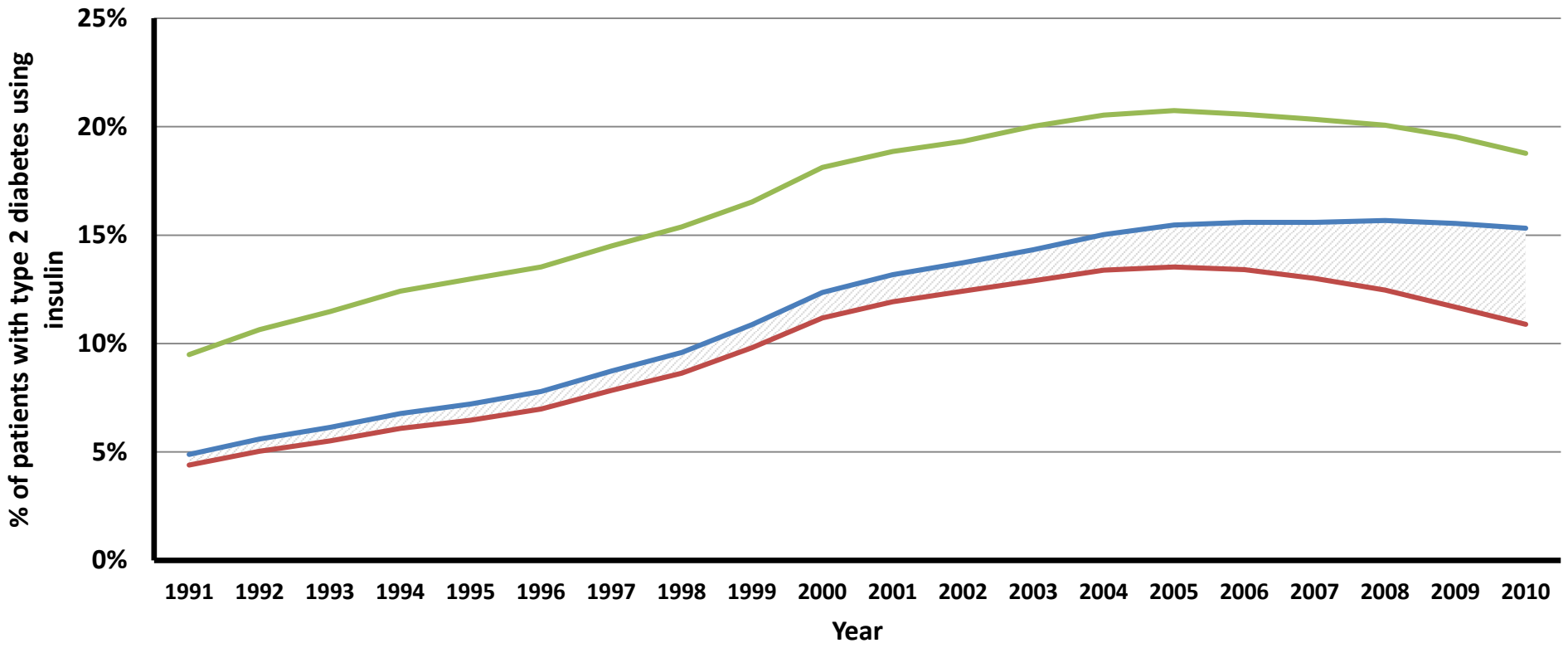
The estimated percentage of patients in CPRD with type 2 diabetes and using insulin increased from 5% in 1991 to 16% in 2009, before decreasing slightly to 15% in 2010 (Figure 6.2). For patients with type 2 diabetes treated with at least one concomitant oral glucose-lowering medicine, 9%, 20%, and 19% of patients were using insulin in 1991, 2009, and 2010, respectively.

The prevalence of type 1 and type 2 diabetes in the UK between 1991 and 2010 is listed in Table 6.5.

Table 6.5 Prevalence of diabetes in the UK 1991–2010

Year	Prevalence of type 1 diabetes	Prevalence of type 2	Overall prevalence of diabetes
1991	0.1%	1.1%	1.4%
1992	0.1%	1.2%	1.4%
1993	0.1%	1.3%	1.5%
1994	0.1%	1.3%	1.5%
1995	0.1%	1.4%	1.6%
1996	0.1%	1.5%	1.7%
1997	0.2%	1.5%	1.8%
1998	0.2%	1.6%	1.9%
1999	0.2%	1.7%	2.0%
2000	0.2%	1.8%	2.1%
2001	0.2%	2.0%	2.2%
2002	0.2%	2.1%	2.4%
2003	0.2%	2.3%	2.6%
2004	0.2%	2.5%	2.8%
2005	0.2%	2.6%	2.9%
2006	0.2%	2.8%	3.1%
2007	0.2%	2.9%	3.3%
2008	0.2%	3.2%	3.5%
2009	0.2%	3.4%	3.7%
2010	0.2%	3.6%	4.0%

Figure 6.2 The percentage of patients with type 2 diabetes using insulin



Red line = percentage of all patients diagnosed with type 2 diabetes using insulin; blue line = percentage of all patients with type 2 diabetes using insulin when the more strict criteria for selecting diet-controlled patients was applied (>1 prescription for a glucose biosensor strip or a Read code for diabetes on diet only); green line = percentage of treated patients with type 2 diabetes using insulin. The shaded section represents the difference between the percentage of patients using insulin when the strict and relaxed criteria are used for the selection of patients with diet-controlled type 2 diabetes.

6.4. Discussion

6.4.1. Main findings

The estimated number of people injecting insulin in the UK increased three-fold over the 20-year study period from 1991–2010. During the same interval, there was a seven-fold increase in the number of people assigned a diagnosis of type 2 diabetes and treated with insulin as against a 30% increase in those assigned a diagnosis of type 1 diabetes. These estimates should, however, be treated with caution because diagnostic classification has changed over the last 20 years and the clinical subdivision of the two types of diabetes may be imprecise. The proportion of those with a diagnosis of type 2 diabetes treated insulin increased from 5% to 15% over the period, reaching a plateau after 2005 (Figure 6.2). Almost all insulin users with type 2 diabetes were treated with an insulin monotherapy regimen in the first decade of observation, whereas two-thirds of insulin users with type 2 diabetes received insulin in combination with at least one other glucose-lowering medication in the second decade of observation.

6.4.2. Comparison with existing literature

A previous study from a UK region reported the prevalence of type 1 diabetes for males and females in 1997 to be 0.4% (95% CI 0.379–0.43%) and 0.28% (95% CI 0.25–3.0%), respectively.[430] They also reported that 12% of patients with type 2 diabetes injected insulin.[430] This estimate is higher than the one calculated for this study, where in 1997 the prevalence of type 1 diabetes was 0.18%, and 15% of patients with type 2 diabetes were estimated to be treated with insulin. A further study based on the population of Poole in Dorset, England, estimated that the overall prevalence of insulin

use was 0.5% in 1996, in comparison with 0.3% calculated for this study.[429] One possible explanation for this was the poor recording of prescriptions in earlier years of the CPRD database. Alternatively, in our study, a gap of longer than 6 months between insulin prescriptions was used to indicate that insulin treatment had been discontinued. This may have led to the exclusion of patients who collected their prescriptions intermittently. US data from the Center for Disease Control and prevention 2011 National Diabetes Fact Sheet suggest that, in 2007–2009, 26% of patients with diabetes were using insulin, 58% were using oral glucose-lowering agents and 16% were diet-controlled only.[13] The corresponding figures for this study are similar with 22% of all patients with diabetes using insulin, 58% using other glucose-lowering drugs and 20% diet-controlled for the same time period.

The prevalence of type 1, type 2 and diabetes overall calculated for this study increased from 0.1%, 1.1% and 1.4% in 1991 to 0.2%, 3.6% and 4.0% in 2010, respectively (Table 6.5). The overall prevalence of diabetes is similar to the prevalence of 4.26% published in 2010 by Diabetes UK, which translated to an estimated 2.8 million people in the UK with diabetes.[420] This increase in the prevalence of diabetes may be due at least in part to more enhanced detection of subclinical type 2 diabetes and increased survival for people with diabetes. Increased survival could account for the increased use of insulin between 1991 and 2010 as more people live long enough to progress to insulin treatment.

A change in the management of people with type 2 diabetes requiring insulin therapy emerged during the study period, where the use of regimens that combined oral glucose-lowering therapies with insulin increased from 13% in the first decade of observation to 52% in the second. A similar pattern has also been reported in the USA:

in 1997, 2.3 million people with diabetes were treated with insulin alone versus 1.1 million people receiving combination therapy. By 2010, 2.8 million people were receiving insulin alone and 2.9 million were on combination therapy.[467] The proportion of people prescribed insulin in combination with metformin increased substantially following the publication of the results from UKPDS in 1998 even though this study did not report results for this combination therapy specifically. Current NICE Guidelines recommend that insulin is added to existing glucose-lowering therapy instead of using insulin alone.[54] In addition, in 2006, EASD and ADA guidelines recommended that insulin should be added to existing metformin therapy rather than switching patients to insulin monotherapy.[470]

Although there has been an increase in the estimated number of insulin users in the UK, there has also been an increase in the number of people in the UK with diabetes. Diabetes UK has published figures to show that the number of people with diabetes in the UK has increased from 1.4 million in 1996 to 2.8 million in 2010.[420] However, the percentage of patients with type 2 diabetes prescribed insulin increased from 5% to 16% between 1991 and 2009 before decreasing slightly to 15% in 2010. Therefore, the increase in the number of insulin users in the UK represents a change in treatment pattern with an increase in the prescribing of insulin for type 2 diabetes. Masso-Gonzalez et al also found that the percentage of prevalent cases treated with insulin increased between 1996 and 2005 from 15.1% to 15.5%. However, this increase was smaller than the increase of 7% to 15% found during the same period in this study.

The proportion of people with type 2 diabetes treated with insulin increased three-fold during the study period, with the sharpest increase occurring during the period 1995 to 2005. The increased use of insulin in type 2 diabetes may reflect influences such as

the publication of findings from the UKPDS in 1998 and recommendations from NICE in 2002 advocating tighter blood glucose control. The results of UKPDS suggested that intensive control of glucose levels using insulin or sulfonylureas reduced the risk of developing microvascular complications and a decrease in the risk of myocardial infarction and death was observed during the ten year follow-up.[67] NICE guidelines recommend a general target for HbA_{1c} levels of 6.5%, although it also suggests that a target of 7.5% when initiating a third line agent such as insulin.[54] Furthermore, the introduction of the QOF, launched in the UK on 1st April 2004[404] may have further promoted the initiation of insulin in people with type 2 diabetes by providing incentives for achieving lower glucose targets. Marketing may have also played a role, particularly following the launch of the basal insulin analogues (insulin glargine in 2000 and insulin detemir were launched in 2004[69]). In addition, long-acting insulin analogues have been associated with a lower risk of hypoglycaemia when compared with compared to NPH insulin[71] and insulin glargine can be administered as a once-daily dose. As regimen complexity and fear of inducing hypoglycaemia have been cited as possible barriers to the initiation of insulin, then overcoming these barriers may have led to the increased prescribing of insulin.

However, the baseline characteristics for type 2 diabetes patients do not support the early initiation of insulin. There was little change in the baseline HbA_{1c} levels at insulin initiation during the study period (10.0%, 9.7%, 9.7% and 9.8% for 1991–1995, 1996–2000, 2001–2005 and 2006–2010, respectively), although these values are for both type 1 and type 2 diabetes. Furthermore, between 2001 and 2007, HbA_{1c} levels for patients with type 2 diabetes remained relatively constant (8.5% in 2001 and 8.4% in 2007), suggesting that more aggressive control of blood glucose was not achieved.[178] Brown and colleagues also found evidence of a delay in the initiation of insulin in type

2 diabetes in a US population of members of the Kaiser Permanente Northwest Region, where the average patient accumulated nearly five HbA_{1c} -years of excess glycaemic burden of more than 8.0% from diagnosis to insulin initiation.[457] During the study period, the age at insulin initiation increased from 52.5 years in 1991–1995 to 58.1 years in 2006–2010, despite a reduction in the age of onset of type 2 diabetes during the same period. However, this may reflect ageing of the population as a whole.

The increase in the prevalence of insulin use was followed by a plateau after 2005 and a small decline in insulin use the last few years of the study. One possible explanation for this is the introduction and increased use of the GLP-1 agonists (exenatide in 2006 and liraglutide in 2009[69]). In 2012, the EASD and ADA produced guidelines recommending a more patient centred approach to type 2 diabetes management, although the recommended HbA_{1c} target was not changed.[7] In addition, the QOF Indicator Advisory Committee has recommended that the target for HbA_{1c} should be increased to 7.5%.[471] Decreasing prevalence of insulin use among people with diabetes has also been observed in the US where the prevalence has fallen from 36% in 1995 to 22% in 2007.[469] In contrast to our study results, the NHS has continued to spend an increasing amount on insulin and the number of insulin items dispensed in England has increased year on year between 2009/10 and 2010/11.[291]

6.4.3. Strengths and weaknesses of the study

This study had several limitations. CPRD GOLD is a large dataset and has been shown to be representative of the population in terms of crude mortality and the age and gender structure.[364,365] However, age-standardised mortality rates are 9–13% lower than the national average, which has been attributed to a healthy user bias and the

exclusion of people with no exact date of death[364] CPRD GOLD is also a very large longitudinal dataset. In a systematic review, Khan and colleagues reported that the positive predictive value for most conditions investigated was more than 50%.[367] However, rates of diabetes and musculoskeletal conditions were underestimated in GPRD.[367] In a more recently conducted systematic review, Herrett and colleagues, reported that the median proportion of cases with a confirmed diagnosis was 89% (range 24–100%).[368] During the study period, the size of the population in CPRD increased dramatically (3.3 to 6.3 million). Therefore, during the earlier study years, the database is likely to be less representative of the UK population. In addition, prescriptions and diagnoses may have been less well recorded in the early stages of the data source. The distinction between type 1 and type 2 diabetes data is always problematic in observational studies, particularly because diagnostic criteria and the coding of diabetes have changed over time. IDDM and NIDDM were the preferred terms prior to 1997; they have now been replaced with the terms type 1 and type 2 diabetes, respectively.[367] In our study, all those with diagnostic codes for only IDDM were included in the group of patients with type 1 diabetes. Inconsistent recording of diabetes diagnosis was a further concern. An age-based distinction (e.g. between those diagnosed before and after age 30) would have potentially been more robust, but our study design did not permit us to ascertain age at first diagnosis for all subjects because it was a prevalence study. Thus, although our study design did permit accurate estimates of total insulin use, the ascribed ratio between type 1 and type 2 diabetes should be interpreted with caution, especially in earlier years. The impact of misclassification may have been to slightly inflate the number of people with type 1 diabetes in earlier years and, correspondingly, to slightly reduce the number of people with type 2 diabetes. The effect would obviously disproportionately impact type 1

diabetes. The overall numbers and the general patterns are thought to be reliable, but people with type 2 diabetes using insulin monotherapy are more likely to remain unclassified than patients prescribed other glucose-lowering drugs. In the last few years, patients with diet-controlled type 2 diabetes have not been routinely prescribed glucose biosensor strips for the self-monitoring of blood glucose.[472] This may have resulted in an underestimation of the diet-controlled type 2 diabetes group with an overestimation of the percentage of patients with type 2 diabetes using insulin.

6.4.4. Conclusion

Between 1991 and 2010, there has been a major increase in the estimated number of people with type 2 diabetes using insulin. However, this does not appear to be a result of the earlier introduction of insulin in response to national guidelines, since the baseline HbA_{1c} level at which insulin is initiated has not fallen over 20 years and has remained high throughout the study period. As baseline HbA_{1c} remained high throughout the study period (approximately 10.0%), this suggests that national policies may not have been fully implemented. The increased use of insulin in type 2 diabetes may therefore represent a true change in the demographics of the type 2 diabetic population with an increase in the proportion of patients with more advanced type 2 diabetes, rather than a change in clinical practice. The rising prevalence of insulin use may reflect both increasing incidence and longer survival of people with type 2 diabetes. However, during the last few years of the study period, a small decrease in the proportion of people with type 2 diabetes treated with insulin was observed, and this reflects the more recent pattern of usage in the US. Further research is required to determine if this trend continues.

There has been a significant change in the management of people with the proportion of people receiving insulin in combination with metformin increasing substantially. This is in line with current evidence and guidelines.

7. Annual cost of insulin to the NHS between 2000 and 2009 and the incremental cost of analogue insulin to the NHS

This chapter is based on the accepted version of the following article: Holden SE, Poole CD, Morgan CL, Currie CJ. Evaluation of the incremental cost to the National Health Service of prescribing analogue insulin. *BMJ Open* 2011;1:e000258.,which has been published in final form at [http://bmjopen.bmj.com/content/1/2/e000258.long].

7.1. Introduction

7.1.1. Background

The number of people diagnosed with diabetes in the UK has risen to 2.8 million,[473–476] with approximately 90% of these having type 2 diabetes.[477] People with type 1 diabetes require insulin from onset, whereas those with type 2 diabetes will tend to be switched to insulin later in the natural history of their disease.[478]

Currently, there are three different types of insulin by molecular origin on the market. From oldest to newest, these are animal insulin, human insulin and analogue insulin. Human insulin was introduced in the 1980s and was thought to be less immunogenic than animal insulin, thus leading to lower antibody titres. However, no clinically relevant differences, in terms of adverse effects or glycaemic control, between animal (particularly purified porcine insulin) and human insulin could be detected.[479] Despite this lack of evidence, human insulin was used routinely and the use of animal insulin declined rapidly.[51,479]

Insulin analogues were developed through structural modification of human-sequence insulin to better mimic the pharmacokinetic profile of endogenous insulin, thereby achieving more optimal onset or duration of action and simpler, more convenient dosing regimens.[51,480] Long-acting insulin analogues can be injected once daily and short-acting insulin analogues injected closer to meal times without affecting post-prandial glucose control.[481] Since their launch, the use of analogue insulin has increased steadily and they have had an increasing impact on the amount of money the NHS spends on diabetes.[482] In England, the annual NIC of analogue insulin in 2004-2005 was £109.8 million (55% of total insulin cost) and by 2009-2010, this had risen to £255.2 million per year (85.3% of the total cost of insulin).[482] The Institute for Quality and Efficiency in Healthcare (IQWiG) in Germany has disputed whether the benefits of analogue insulin are sufficient to outweigh their increased cost.[483,484] In the UK, NICE recommends the use of human NPH insulin first-line. Insulin glargine is only recommended in specific circumstances, and not as first-line therapy.[485]

7.1.2. Aims and objectives

The aim of this study was to characterise the pattern of insulin prescriptions dispensed between 2000 and 2009, inclusively, for the whole of the UK, and to evaluate the marginal financial cost to the NHS of using analogue insulin instead of its equivalent human insulin preparation. This analysis formed the basis of the cost-saving estimates presented by the *BMJ* and Channel 4 News.[486]

7.2. Methods

The data underpinning this study were open-source data from the four prescription pricing agencies for England,[375] Northern Ireland,[376] Scotland,[377] and Wales.[378] The PCA for England, Northern Ireland, and Wales describe the quantity and NIC of all NHS prescriptions dispensed in primary care in the constituent country. The NIC refers to the cost of the drug before any discounts, and does not include any dispensing costs or fees.[487] The PCA for Scotland details gross ingredient cost (GIC), which is equivalent to NIC in the PCAs for England, Northern Ireland, and Wales.[488] The PCAs for the four countries from 2000 to 2009 were then combined[378]. Data were grouped into insulin types according to their molecular origin (analogue, human-sequence and animal-sequence) and also into individual insulin types (insulin soluble, insulin isophane, insulin zinc suspension mixed, insulin zinc suspension crystalline, biphasic isophane insulin, protamine zinc insulin, insulin aspart, insulin lispro, insulin detemir, insulin glargine, biphasic insulin aspart, biphasic insulin lispro, and insulin glulisine). For the Welsh data from 2000 to 2004, it was necessary to calculate the quantity of each type of insulin dispensed from the NIC per unit quantity from the PCA for England, Scotland, or Northern Ireland, since the Welsh PCA data did not include this information until 2005. If the drug name in the PCA did not specify a presentation i.e. vial, pre-filled pen or cartridge, then it was assumed to be a vial.

All costs were adjusted for inflation, and they are reported in UK pounds at 2010 prices using the gross domestic product deflator published by HM Treasury.[489] The incremental cost of analogue insulin was calculated by summing the NIC of analogue insulin and then subtracting the cost of dispensing the same volume of insulin as insulin of human origin.

The incremental cost of analogue insulin was also calculated by assuming that if patients prescribed analogue insulin had alternatively received human insulin, they would still have received the same presentation i.e., a vial, a prefilled pen, or cartridge for a reusable pen device, since patients and clinicians favour the ease-of-administration offered by pen devices.[490,491] Using data from a previous analysis of all prescribing costs for diabetes throughout the UK,[178] we were further able to estimate the relative volumes of analogue and human insulin prescribed by the type of diabetes.

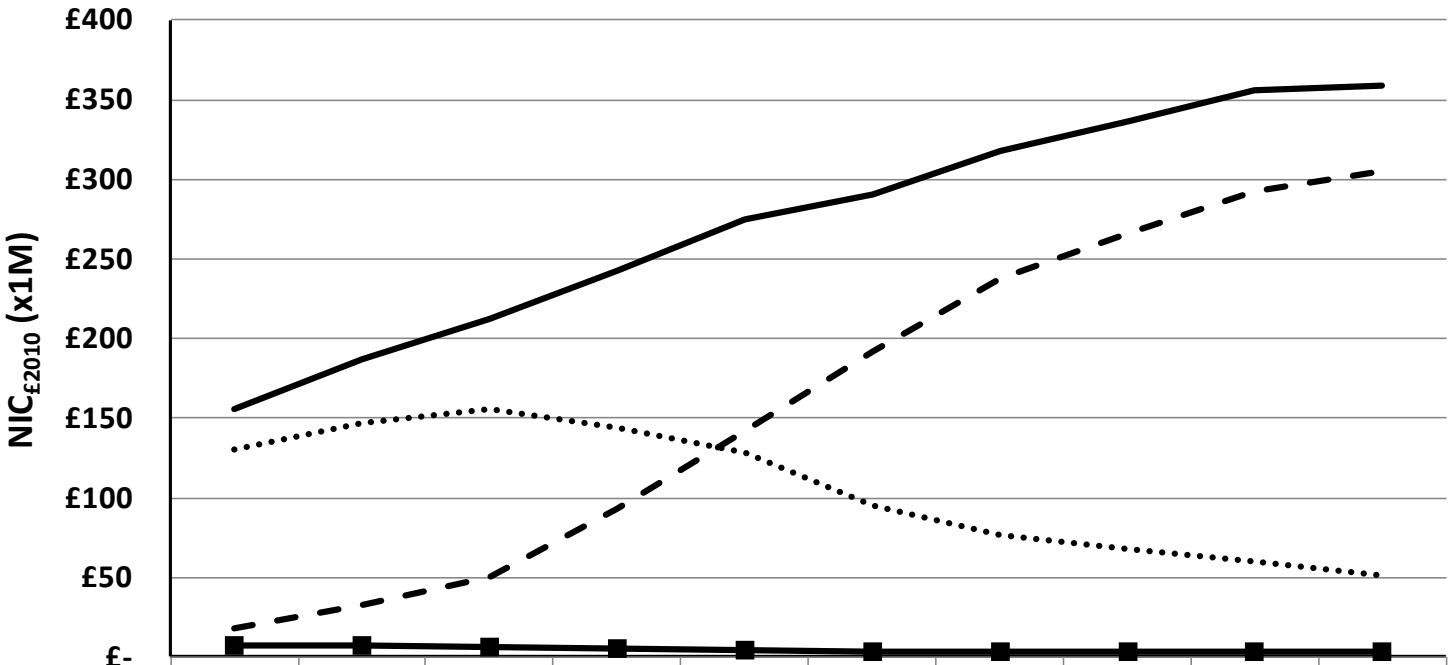
7.3. Results

7.3.1. Net ingredient cost of insulin in the UK, 2000–2009

Over the 10-year period the NHS spent a total of £2,732 million (M) on insulin prescriptions. Prescriptions for analogue insulin accounted for £1,629M (59%), human insulin £1,056M (39%) and animal insulin £47.2M (2%).

The annual, total cost of insulin increased from £156M in 2000 to £359M in 2009, a 130% increase (Figure 7.1). In 2000, the annual cost of analogue insulin was £18.2M, which represented only 12% of total insulin cost, but the cost of human insulin was £131M or 84% of the total cost of insulin. From 2005, by which time all the currently marketed insulin analogues had been launched—spending on analogue insulin increased from £192M (66% of total insulin costs) to £305M (85% of total insulin cost) in 2009. During the same period, the annual cost of human insulin fell from £95.3M (33%) to £51.1M (14%). The cost of animal insulin per year also decreased from £7.42M (5%) in 2000 to just £3.07M (1%) in 2009.

Figure 7.1 The total annual cost of insulin prescriptions for the UK, 2000–2009



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Total	156.1	186.9	212.5	242.3	274.6	290.6	317.5	336.3	355.8	359.1
Analogue	18.2	32.4	50.2	92.9	142.0	191.9	238.0	265.8	292.4	304.9
Human	130.5	147.4	155.9	143.8	127.9	95.3	76.5	67.6	60.1	51.1
Animal	7.4	7.1	6.4	5.6	4.7	3.5	3.0	3.0	3.4	3.1

7.3.2. Incremental cost of analogue insulin in the UK, 2000–2009

The unit cost of each insulin preparation is listed in Table 7.1. Overall, analogue insulin cost on average £2.31 per ml, and was therefore 47% more expensive than human insulin at £1.57 per ml. In 2009, the mean NIC per ml was £1.27 for human insulin and £2.25 for analogue insulin. The NIC per ml of human and analogue insulin peaked between 2003 and 2004, respectively. The 2009 NIC per ml was a 27% decrease for human insulin and a 7% decrease for analogue insulin from 2004 (Table 7.2).

Table 7.1 Net ingredient cost (NIC) and volume of analogue and human insulin by presentation for the UK, 2000–2009

Insulin formulation	$NIC_{£2010}$	Volume (ml)	%	$NIC_{£2010}$/ml
Analogue insulin	£1,628,566,983	706,275,942		£2.31
Pen	£705,567,792	285,036,913	40%	£2.48
Penfill	£839,695,265	362,630,874	51%	£2.32
Vial	£83,303,925	58,608,155	8%	£1.42
Human insulin	£1,055,956,518	671,922,946		£1.57
Pen	£218,790,437	117,962,069	18%	£1.85
Penfill	£645,030,389	373,850,061	56%	£1.73
Vial	£192,135,692	180,110,816	27%	£1.07

Table 7.2 Average net ingredient cost (NIC) per millilitre in the UK, 2000–2009

Year	NIC£2010/ml for human insulin	NIC£2010/ml for analogue insulin
2000	£1.60	£2.24
2001	£1.69	£2.24
2002	£1.76	£2.25
2003	£1.75	£2.33
2004	£1.74	£2.41
2005	£1.38	£2.36
2006	£1.37	£2.34
2007	£1.37	£2.27
2008	£1.35	£2.30
2009	£1.27	£2.25

These unit costs translated into an estimate of the maximum, annual, incremental cost of dispensing analogue insulin assuming that all analogue prescriptions dispensed could have been alternatively prescribed as human insulin. Assuming 100% conversion, the annual incremental cost of analogue insulin increased from £5.18M in 2000 to £133M in 2009 (Table 7.3). Overall, for the 10-year period, the total incremental cost of analogue insulin was £625M at 100% conversion and £312M at 50% conversion. Between 2005 and 2009, the incremental cost of analogue insulin was £538M at 100% conversion and £269M at 50% conversion.

Table 7.3 Incremental cost of analogue insulin in the UK, 2000–2009

Year	Incremental cost (£2010) (assuming 100% conversion analogue to human insulin)	Incremental cost (£2010) (assuming 50% conversion analogue to human insulin)
2000	£5,183,001	£2,591,500
2001	£8,065,849	£4,032,924
2002	£10,795,155	£5,397,578
2003	£23,143,753	£11,571,877
2004	£ 39,529,331	£19,764,666
2005	£79,448,570	£39,724,285
2006	£98,317,347	£49,158,673
2007	£106,139,197	£53,069,598
2008	£121,376,170	£60,688,085
2009	£132,895,201	£66,447,601
Total for 2000 to 2009	**£624,893,574**	**£312,446,787**

7.3.3. Estimated cost by diabetes type

People with type 2 diabetes accounted for an estimated £86.0M of NHS expenditure in 2000 on human and analogue insulin, increasing to £229M (+166%) in 2009. For type 1 diabetes these values were £62.7M and £127M respectively (+103%). Over the whole period, the total cost of insulin prescribing for type 2 diabetes was £950M for insulin analogues and £708M for human insulin (Table 7.4). The incremental cost of analogue

insulin for patients with type 2 diabetes was estimated at £306M at 100% conversion and £153M at 50% conversion.

7.3.4. Incremental cost of analogue insulin in the UK taking insulin presentation into account, 2000–2009

Human insulin is more likely to be dispensed as a vial when compared to insulin analogues, which are typically administered as a pen device (Table 7.1). In calculating the incremental cost of analogue insulin, when assuming that all those receiving analogue insulin had been dispensed human insulin instead but the presentation remained the same i.e., vial, pen or a pen-fill device, then the incremental cost of analogue insulin in the UK between 2000 and 2009 would have been £271M at 50% conversion and £541M at 100% conversion, compared with £625M at 100% conversion (Table 7.3) if insulin presentation is not taken into account.

Table 7.4 Estimated change in net ingredient cost (NIC) and volume of human and analogue insulin prescribed to patients with type 1 and type 2 diabetes in the UK, 2000–2009 cost

Year	$NIC_{£2010}$ for type 1 diabetes		$NIC_{£2010}$ for type 2 diabetes		Volume (ml) for type 1 diabetes		Volume (ml) for type 2 diabetes	
	Total analogue	Total Human	Total analogue	Total Human	Total analogue	Total Human	Total analogue	Total Human
2000	£11,228,382	£51,444,334	£6,923,103	£79,075,954	5,038,092	33,056,509	3,050,474	48,350,233
2001	£17,858,968	£55,211,316	£14,564,748	£92,155,033	8,001,813	33,577,135	6,443,335	53,816,755
2002	£25,764,159	£57,242,261	£24,410,582	£98,670,067	11,520,222	33,039,547	10,827,941	55,441,680
2003	£45,316,250	£49,420,126	£47,585,514	£94,338,575	19,667,109	28,663,444	20,145,487	53,383,153
2004	£65,066,374	£40,577,834	£76,937,127	£87,354,455	27,296,077	23,712,414	31,672,369	49,905,829
2005	£82,462,748	£28,231,889	£109,393,916	£67,039,353	35,341,564	21,196,772	45,841,398	47,609,677
2006	£97,342,547	£21,284,207	£140,625,903	£55,238,238	42,215,106	15,771,316	59,651,444	40,046,916
2007	£105,277,447	£17,662,770	£160,494,779	£49,900,346	46,896,096	13,048,606	70,028,562	36,438,609
2008	£113,178,916	£14,924,884	£179,215,091	£45,134,839	49,542,256	11,113,432	77,455,050	33,486,730
2009	£114,597,696	£12,375,736	£190,322,726	£38,711,902	51,543,528	9,734,567	84,098,018	30,547,933
Total	**£678,093,486**	**£348,375,355**	**£950,473,489**	**£707,618,762**	**297,061,863**	**222,913,742**	**409,214,078**	**449,027,514**

7.4. Discussion

7.4.1. Main findings

Since their launch, insulin analogues have had an increasingly noteworthy impact on the amount of resource used to manage diabetes. The inflation-adjusted, annual cost to the NHS of insulin increased from £156M in 2000 to £359M in 2009 (a two-fold increase). During the same period, NHS spending on analogue insulin increased from £18M (12% of total insulin cost) per year to £305M (85% of total insulin cost) and at the same time, NHS annual spending on human insulin fell from £130M (84%) to £51.1M (14%). If all dispensations for analogue insulin between 2000 and 2009 had used the equivalent human insulin, we estimate the NHS would have saved £625M.

7.4.2. Comparison with existing literature

The pharmacokinetic profiles of insulin analogues do appear to improve glycaemic control and reduce the incidence of hypoglycaemia (particularly nocturnal), compared with human insulin equivalents.[71,73]Long-acting insulin analogues have a longer duration of action and, in the case of insulin glargine, no peak plasma concentrations when compared with NPH insulin.[492,493] Short-acting insulin analogues have a lower tendency for self-association, faster absorption and higher peak plasma concentrations that are achieved more quickly than with soluble human insulin.[494] This can result in improved dosing schedules for the insulin analogues. Additionally, insulin detemir has been associated with less weight gain than other long-acting insulin formulations.[175]

A Cochrane systematic review compared short-acting insulin analogues with regular human insulin and found a small, statistically significant improvement in glycaemic

control for people with type 1 diabetes but no benefit in patients with type 2 diabetes.[73] Both analogue and human insulin were associated with similar levels of hypoglycaemia.[73] The Cochrane review comparing long-acting insulin analogues with NPH insulin in type 2 diabetes concluded that there was no evidence of a beneficial effect in terms of glycaemic control and only a minor benefit in terms of nocturnal hypoglycaemic events.[71] The longest trial comparing insulin glargine and NPH insulin found that, over five years' observation, there was a similar progression to retinopathy but less improvement in the HbA_{1c} level for insulin glargine as the mean HbA_{1c} change from baseline was -0.55% with insulin glargine and -0.76% with NPH insulin (the least square mean difference was 0.21 higher with NPH insulin, 95% CI 0.06–0.35; p=0.0053).[495] Epidemiological data from the UK indicates that, despite general improvements in the provision of diabetes care and the introduction of insulin analogues, there has been no observable improvement in HbA_{1c} levels for patients with type 2 diabetes treated with exogenous insulin.[60] There is currently no systematic means of measuring the clinical benefits associated with analogue insulin, such as rate of symptomatic or nocturnal hypoglycaemia, making it difficult to judge the real-world cost effectiveness of these drugs. However, an analysis of open-source HES data shows that growth in hospital admissions for hypoglycaemia has exceeded growth in the prescribing of insulin.[496]

The cost effectiveness of analogue insulin is likely to vary depending on the type of diabetes, the clinical characteristics of the individual patient and the type of analogue insulin in question. For example rapid-acting insulin analogues in patients with type 1 diabetes are likely to be a cost-effective use of finite healthcare resources.[497] In the UK, NICE has recommended that insulin glargine and rapidly-acting insulin analogues

are an option for the control of blood-glucose in patients with type 1 diabetes but has stated that human insulin should be prescribed as first-line therapy and long acting analogues such as insulin glargine and premixed insulin should only be used in certain specific circumstances.[55,70] NICE has determined that insulin glargine borders on being cost effective at current willingness to pay thresholds in people with type 1 diabetes but that it is not cost effective in type 2 diabetes.[485] In Germany, IQWiG has stated that there are insufficient studies investigating the long-term effects of using insulin analogues and that rapid-acting and long acting insulin analogues have no proven superiority over human insulin for type 1 and type 2 diabetes.[483,484,498,499] A similar recommendation has been made by Canadian Agency for Drugs and Technologies in Health (CADTH) where NPH insulin is recommended as first line and the use of insulin analogues are only recommended for patients who experience significant hypoglycaemia.[500] If bolus insulin therapy is required, CADTH again recommends human insulin as first line therapy for patients with type 2 diabetes but rapid-acting insulin analogues can be used first line in type 1 diabetes sufferers.[500] In New Zealand, insulin glargine and insulin detemir were only recommended with special authority criteria, although there is now agreement to widen access to insulin glargine.[501,502] In a study of US patients with private insurance, a large increase in the prevalent use of insulin analogues has been observed.[503] The WHO has found that some countries spend a significant amount of their drug budget on insulin analogues and there are problems with the lack of availability of human insulin.[504] They have advised that insulin analogues offer no clinical advantage over human insulin and suggested that insulin analogues may not be cost-effective in low- and middle-income countries.[504] In a recent feature article for the *BMJ*, it was suggested that insulin remains unaffordable

in many countries and even though insulin is off-patent, the availability of generic products is limited.[505]

The popularity of the insulin analogues could be due in part to successful marketing. Some of the manufacturers of insulin analogues also provided professional support to GPs at the same time that their analogue insulin was marketed, although this was not conditional on the doctor prescribing their insulin.[486] Insulin analogues were also available in new devices that may be more appealing to patients and easier to use than the devices used to administer human insulin.[486] The fact that 40% of analogue insulin was prescribed as a prefilled pen device compared with just 18% for human insulin supports this.

As insulin manufacturers focus on newer, patentable insulin analogue products, they have withdrawn some of their older human insulin products, where a move to patented insulin products has notable commercial benefits to manufacturers. Patients using these products have required conversion to an alternative product, which might contain either human insulin or an insulin analogue. In 2005, Novo Nordisk discontinued Actrapid penfills and recommended Novorapid as an alternative product. They also withdrew Insulatard Flexpen and Monotard from their range of human insulin at the same time.[506] Since the withdrawal of Mixtard 30 at the end of 2010, the 90,000 users will have been changed to an alternative product.[72] It will be interesting to repeat this study to assess whether these patients have been switched to human insulin (the equivalent product is Humulin M3) or indeed to analogue insulin. The Drug and Therapeutics Bulletin has estimated that if all the users of Mixtard 30 were switched to Novomix 30, it would result in an increase in cost of £9 million to the NHS in England alone.[72]

The increase in the annual inflation-adjusted NHS cost between 2000 and 2009 can be partly accounted for by the increase in prevalence of diabetes in the UK during this time. In 1996, it was estimated that 1.4million people in the UK had diabetes.[420] By 2004, this figure had risen to 1.8million[507] and by 2009, 2.6 million people in the UK had diabetes.[508] People with type 2 diabetes can be managed with one or more of diet, oral glucose-lowering medication or insulin where as people with type 1 diabetes are dependent on exogenous insulin. However, the estimated volume of analogue and human insulin dispensed to patients with type 2 diabetes is far greater than for type 1 diabetes. This can be explained by the prevalence of type 2 and type 1 diabetes in the UK. It has been estimated that approximately 90% of people with diabetes in the UK have type 2 diabetes. It can be further explained by the nature of type 2 diabetes. It is characterised by insulin resistance. Patients with type 2 diabetes are more likely to be overweight or obese than people with type 1 diabetes.[509] Therefore, people with type 2 diabetes using insulin often receive higher insulin doses. Furthermore, results from UKPDS may have influenced the increased prescribing of insulin to people with type 2 diabetes so that lower HbA_{1c} levels could be obtained.[112]

7.4.3. Strengths and weaknesses of the study

This study had inherent limitations. The calculation of the incremental cost of analogue insulin was based on the assumption that the same volume of insulin would be prescribed if patients were switched from analogue to human insulin. The PCA for Wales from 2000 to 2004 did not contain the quantity of insulin dispensed, which was necessary to calculate the incremental cost. The quantity, therefore, needed to be calculated from the NIC per quantity figures from the PCAs for England, Scotland, and

Northern Ireland. However, certain products in the Welsh PCA were not available for the other regions for the same year, so figures from the previous years had to be used and adjusted for inflation. Some drugs were listed only under their generic name in the Welsh PCA and so a weighted-average NIC per quantity was taken from the branded products in the English PCA. The same approach was taken when the drug name description did not specify whether the cartridge size was 1.5ml or 3ml (when these were the only cartridge sizes on the market). In addition there were two drug names, Human Actraphane and Human Protaphane vials, that had no matches in any of the other PCAs for any year. These are Novo Nordisk products, which tend to carry the same cost per unit depending on whether they are vial, penfill, or prefilled pen and are not dependent on what type of human insulin is in the device. Therefore, the NIC per quantity used for these two products was the NIC per quantity of the other Novo Nordisk vials. These assumptions were unlikely to have impacted upon the estimates as a whole, since the NIC and volume relating to these products and country was only small.

Another limitation was that the PCA only informs us about how much of each type of insulin was dispensed; thus, there was no way of determining how much insulin was dispensed to people with type 2 diabetes specifically. However, it is likely that the level of type 1 diabetes remained relatively constant over the study period, while the number of people with type 2 diabetes is known to have increased considerably.[416]

The assumption that all patients using insulin analogues could be equally well treated with human insulin is also likely to be unrealistic. Dr Adler, chair of the NICE guidance committee, has suggested that 90% of patients with type 2 diabetes could receive human insulin instead of long-acting insulin analogues with around two-thirds of these

patients remaining on human insulin.[486] At this moment, however, there is no definitive figure of how many people with diabetes could have received human insulin instead of analogue insulin.

This study did not take into account any other savings that could have been made as a result of treatment with insulin analogues as opposed to human insulin. It is not known whether the use of insulin analogues would lead to a reduction in hospital admissions for hypoglycaemia, reduced prescribing of products used to treat hypoglycaemia or test strips for glucose monitoring. In addition, reduced dosing frequency for the long-acting insulin analogues may also lead to a reduction in the associated equipment required for injecting insulin, for example needles, and an improvement in patient compliance.

7.4.4. Conclusion

At the macroeconomic level, we know that the rise of insulin analogues has had a substantial financial impact on the NHS. Despite the wholesale shift to analogue insulin in high-income countries, there is a lack of literature on the long-term efficacy and safety of the insulin analogues. The methodological rigor of previous RCTs comparing human insulin with insulin analogues has been criticised, especially the over reliance on proxy measures of outcome as the primary endpoints.[71,73,504] RCTs of a longer duration are required to demonstrate whether insulin analogues are superior to human insulin for long-term patient-important outcomes, such as mortality, morbidity and quality of life. Until such evidence is available, adherence to prescribing guidelines would reduce the cost of prescribing insulin in diabetes.

8. Glucose-lowering with exogenous insulin monotherapy in type 2 diabetes: dose association with all-cause mortality, cardiovascular events, and incident cancer

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8.1. Introduction

8.1.1. Background

The number of people with type 2 diabetes treated with insulin in the UK increased from 37,000 in 1991 to 277,000 people in 2010,[422]and at considerable financial cost.[510] Although the use of insulin monotherapy in type 2 diabetes has decreased since 1991, it has been estimated that 37% of people with type 2 diabetes received insulin monotherapy in 2010.[422]

Insulin is recommended as third-line therapy when metformin and sulfonylurea, where indicated, have failed to maintain glucose control.[55] There are few RCTs that compare the use of insulin to alternative glucose-lowering regimens in type 2 diabetes. Whilst insulin has a theoretically unlimited potential to lower blood glucose, there are now a

range of observational studies that have elicited a J-shaped association between glucose control and all-cause mortality and other serious outcomes, showing that the optimal HbA_{1c} level is between 7% to 7.5% [60,223,224,511,512]. The UKPDS demonstrated that intensive control of blood glucose reduced microvascular risk. However, it was not until after the 10-year follow-up that the cardiovascular benefits associated with intensive glucose were detected [67,112]. Meta-analyses of RCTs have shown that intensive glucose control did not significantly affect the risk of all-cause mortality or cardiovascular events [201,202]. In addition, several epidemiological studies have reported an association between insulin use and all-cause mortality and serious adverse events in people with type 2 diabetes [60,61,223,255].

A recently published study demonstrated that when compared with other glucose-lowering regimens, there was an increased association between insulin and all-cause mortality, MACE, cancer and other outcomes in people with type 2 diabetes, but insulin dose was not accounted for in this study [61]. A recent study in the *BMJ* found that insulin treatment in people with type 2 diabetes when included as a covariate in a multivariable model of all-cause mortality, had an aHR of 3.42 (2.61–4.48) [513]. A legitimate criticism of these and other epidemiological studies is the potential for confounding by indication or channelling bias. That is, those treated with insulin are at a more advanced stage in the natural history of the disease or they have phenotypic characteristics that require a switch to insulin. However, if a dose association exists in people with type 2 diabetes treated with insulin, particularly insulin monotherapy, this could help to reduce this risk of this bias.

8.1.2. Aims and objectives

The aim of this retrospective cohort study was, therefore, to determine if there was an association between insulin dose and all-cause mortality, incident MACE, and incident cancer in people with type 2 diabetes.

8.2. Methods

8.2.1. Data source

The data used for this study came from the CPRD.[427] CPRD contains pseudonymised data collected from the daily record keeping of participating primary-care physicians in the UK. These data include patient demographics, consultations, medical history, test results, referrals, and prescriptions. CPRD is broadly representative of the UK population and contains over 12 million patients registered at 660 practices. For a proportion of these practices in England, CPRD records have been linked to NHS HES. The data extract used in this study contains records up to January 2013.

Approval for this study was granted by the CPRD ISAC (reference number 11_017).

8.2.2. Patients

Patients with type 2 diabetes were selected if their records were classed by CPRD as being of 'acceptable' research quality and if at least one of the following criteria applied: more than one diagnostic record exclusively for type 2 diabetes; prescriptions for at least two different classes of glucose-lowering medication other than insulin; or one diagnostic code for type 2 diabetes (irrespective of any records for conflicting or unspecific diabetes diagnoses) plus prescriptions for at least one glucose-lowering medication excluding insulin. Patients were only included if they had received their first prescription for insulin after 1st January 2000 and were receiving insulin monotherapy. This was because of potential confounding by concomitant metformin in particular. The study index date was defined as the date of first insulin prescription,

and cases were required to have a wash-in period of at least 365 days from the later of the patient's registration date and CPRD's practice 'up-to-standard' date.

Patients were excluded from the analysis if they had any record for secondary diabetes. Patients with a history of large vessel disease (defined as prior myocardial infarction [MI], stroke, angina, and or coronary revascularisation) or cancer were excluded from analyses in which MACE or cancer were the respective endpoints.

8.2.3. Study endpoints

The primary outcomes for the study were all-cause mortality; incident MACE, defined as myocardial infarction (MI), stroke, or cardiovascular death; and incident cancer (excluding non-melanoma skin cancer). For patients who had progressed to an event, the censor date was defined as the patient's date of death, cancer, or MACE, provided that the event date recorded was no more than 90 days after the end of recorded data, the date of regimen change (including drug cessation or additional drug inclusion), or the date of their last prescription for insulin. Otherwise the cases were censored. The censor date was defined as the earliest of: the end of a patient's recorded data (the earlier of their transfer-out date or the end of the current CPRD data extract); or 90 days after their date of transfer to an alternative glucose-lowering regimen (including the addition of any other concomitant glucose-lowering medication); or their last prescription for insulin.

8.2.4. Estimation of insulin dose

Unlike many prescriptions for glucose-lowering medications, dose is rarely specified when prescribing insulin. Therefore weight-standardised daily insulin exposure had to be estimated from the volume of insulin prescribed as follows. First, the number of international units prescribed was estimated for each insulin prescription issued during the study period. Conflicting information existed for some prescriptions recorded in CPRD; therefore decision rules were devised in order to maintain a consistent approach (Appendix 2). The number of international units for each prescription was divided by the nearest recorded weight measurement. For each patient, cumulative average insulin dose was calculated on a yearly basis by dividing the sum of the international units per kg (units/kg) represented by the insulin prescriptions received between the index date and the end of the specific year by the number of days observed from the index date to the end of the same year. For patients with an incomplete year of observation, the denominator was the number of days the patient had been receiving prescriptions between the first and last prescription for insulin plus the days between the penultimate and last prescription. Patients were excluded from the analysis if the volume of insulin prescribed could not be determined for one or more prescriptions, there was no recorded weight measurement, or their estimated average insulin dose across the follow-up period was greater than 4 units/kg/day. Only patients with at least two prescriptions for insulin were included as this was a requirement for the calculation of daily dose. Patients with a gap longer than 180 days between prescriptions for insulin were assumed to have stopped taking their insulin and then restarted. In order to avoid an immortal time bias due to the exclusion of people with only one prescription for insulin (thereby ensuring that no patients could

die before their second insulin prescription), only those patients with at least 180 days' follow-up were included in the study. This was because a patient's first and second insulin prescription could be between 1 and 179 days apart.

8.2.5. Statistical methods

Time to each clinical endpoint was evaluated using Cox proportional hazards modelling. The index date for the modelling was taken as the first prescription for insulin plus 180 days. People with events (cancer or MACE) prior to this date were excluded from the relevant analysis. The following baseline covariates were identified *a priori* and included in the Cox proportional hazards model: age, serum creatinine, BMI, duration of diabetes, index year, Charlson morbidity index [374], and the number of GP contacts in the year prior (an alternative measure of morbidity) as continuous covariates, and HbA_{1c} (quartiles), exposure to prior lipid-lowering therapy, prior anti-platelet therapy, prior antihypertensive therapy, gender, insulin regimen, history of cancer or large vessel disease, and smoking status as categorical variables. Many of these covariates have been identified previously as potential predictors of mortality in people with type 2 diabetes [61]. However, index year was added to account for differences in clinical practice over the study period. Where a patient had no HbA_{1c} measurement in a 12-month period, the last observation was carried forward. Missing baseline values for serum creatinine, HbA_{1c}, and BMI were imputed using multiple imputation.

Total cumulative weight-standardised insulin exposure was estimated for each subsequent year following insulin initiation and analysed as a time-dependent continuous variable updated annually. Cumulative insulin exposure has been modelled

previously using a different method for calculating dose [255] and was chosen for this study primarily because of the postulated mechanism by which hyperinsulinaemia is related to cancer [514] and cardiovascular morbidity [182,515]. In addition, cumulative insulin exposure is less sensitive to changes in the collection of prescriptions just prior to an event or limitations in the calculation of insulin exposure in the final (part) year of patient follow-up. However, average annual weight-standardised insulin exposure, average annual weight-standardised insulin exposure modelled with a lag time of one year, and average weight-standardised insulin exposure in the first year after the index date were also investigated in a sensitivity analysis (the latter two were modelled to address a potential bias that insulin dose may have changed markedly prior to an event of interest).

The proportional hazards assumption for the main overall models was tested by examining the Pearson correlation between Schoenfeld residuals and the rank of survival time for cases that had progressed to death. Interactions with time were used to assess the proportional hazards assumption of the extended Cox model. A test of heterogeneity between subgroups was conducted for each subgroup analysis using interactions between the subgroup covariate and study arm. Baseline differences between cohorts were assessed by univariate analysis appropriate to the distribution of the parameter. All analyses were carried out using SPSS.

8.3. Results

8.3.1. Numbers of cases and total follow-up

We identified 6,484 eligible subjects with type 2 diabetes who progressed to insulin monotherapy as their first exposure to insulin (Table 8.1). These subjects were followed up for an average of 3.3 years (median 2.3), representing a total follow-up period of 21,310 years.

8.3.2. Baseline characteristics

The overall, average age at baseline was 64.3 (median 67.0) years and 56% of subjects were male. The mean (SD) estimated prescribed insulin dose was 0.75 (0.40) units/kg/day. The distribution of estimated insulin dose is illustrated in Figure 8.1. In order to show how the baseline characteristics varied across the range of estimated insulin doses, these are detailed across insulin dose quartiles (Table 8.1).

There were notable differences across the four dose groups. The parameters that varied in a largely consistent gradient across the estimated dose values and that also achieved significance at the conventional level included the proportion of males (from 63% in the lowest estimated insulin dose quartile to 51% in the highest, $p<0.001$), age at baseline (65.0 years to 63.4 years respectively, $p=0.004$), diabetes duration (5.2years to 6.8 years respectively, $p<0.001$), existing large vessel disease (30% to 25% respectively, $p=0.004$) and HbA_{1c} (9.2%, 9.8%, 9.9%, and 9.9% respectively, $p<0.001$). Notable parameters where values were less consistent across estimated dose groups included serum creatinine (highest value 99.0 µmol/l, lowest 91.0 µmol/l, $p<0.001$) and BMI (highest value 29.0 kg/m^2, lowest 27.9 kg/m^2, $p<0.001$). In addition, median

Charlson index was higher in the lowest estimated insulin dose quartiles (3 versus 2, p=0.004). There was a difference in the profile of the insulin regimen used across these groups; for example, in the lowest dose group 64% were treated throughout with a premixed insulin regimen, versus 49% in the highest dose group (overall p<0.001).

8.3.3. Numbers of outcome events and crude event rates

After people with prior events were excluded where relevant, the numbers of events of interest were as follows: 1,110 deaths, 342 incident MACE, and 382 incident cancers, with respective rates of 61.3, 26.4, and 24.6 events per 1,000 person years. The unadjusted rates of these events by insulin dose group, using each individual's mean estimated insulin dose for the first year following the index date, are detailed in Figure 8.2.

8.3.4. Risk of all-cause mortality

There was an association between estimated insulin dose and the risk of all-cause mortality. The aHR in relation to an increase in estimated insulin dose of 1 units/kg/day was 1.54 (1.32–1.78, Figure 8.3). The results of a sensitivity analysis in which different estimates of insulin dose were included in the Cox model are presented in Table 8.2.

There was no evidence of a difference in treatment effect between subgroups (test for heterogeneity: p>0.05 for all subgroups).

Table 8.1 Baseline characteristics by average estimated insulin dose over the study period

Parameter	Estimated prescribed insulin dose quartile (units/kg/day)									All identified study patients	
	0.074–0.479		0.480–0.666		0.667–0.913		0.914–3.884		p-value		
Number of people, n (%)	1,622	(25%)	1,624	(25%)	1,616	(25%)	1,622	(25%)		6,484	
Males, n (%)	1,017	(63%)	910	(56%)	887	(55%)	829	(51%)	<0.001	3,643	(56%)
Age at index, mean (median), years	65.0	(68.0)	64.7	(67.0)	63.9	(66.0)	63.4	(65.0)	0.004	64.3	(67.0)
HbA_{1c}, mean (%)[a]	9.1	(2.2)	9.6	(2.1)	9.9	(2.2)	9.9	(2.2)	<0.001	9.6	(2.2)
Systolic blood pressure, mean (SD), mmHG[a]	135.9	(19.3)	135	(19.8)	135.3	(19.6)	136.3	(19.5)	0.305	135.6	(19.5)
Smoking status[b]:									0.126		
Non-smoker, n (%)	600	(37%)	619	(38%)	669	(41%)	661	(41%)		2,549	(39%)
Ex-smoker, n (%)	686	(42%)	680	(42%)	626	(39%)	655	(40%)		2,647	(41%)
Current smoker, n (%)	336	(21%)	325	(20%)	321	(20%)	306	(19%)		1,288	(20%)
Triglycerides, median (IQR), mmol/l[a]	1.7	(1.2–2.5)	1.7	(1.2–2.5)	1.9	(1.3–2.8)	2.1	(1.3–3.2)	<0.001	1.8	(1.2–2.7)
HDL, median (IQR), mmol/l[a]	1.2	(0.9–1.4)	1.2	(1.0–1.5)	1.2	(1.0–1.4)	1.1	(0.9–1.4)	0.003	1.2	(0.9–1.4)
Total cholesterol, mean (SD), mmol/l[a]	4.7	(1.2)	4.7	(1.2)	4.8	(1.3)	4.7	(1.2)	0.192	4.7	(1.2)
Serum creatinine, median (IQR), µmol/l[a]	99	(79–137)	95	(76-128)	96	(77–126)	91	(75–121)	<0.001	95.0	(77.0-128.0)
DM duration, median (IQR), years[c]	5.2	(1.6–10.2)	6.3	(2.2–11.1)	6.7	(2.5–12.1)	6.8	(2.9–11.1)	<0.001	6.2	(2.2–11.1)
BMI, mean (SD), kg/m^{2a}	29.0	(6.0)	27.9	(5.9)	28.2	(6.0)	27.9	(5.8)	<0.001	28.2	(5.9)
Weight, mean (SD), kg	83.3	(18.0)	78.8	(17.4)	78.9	(18.4)	77.9	(18.5)	<0.001	79.7	(18.2)
Glucose-lowering therapies year prior:											
Metformin	864	(53%)	964	(59%)	985	(61%)	1,076	(66%)	<0.001	3,889	(60%)
Sulfonylureas	1,067	(66%)	1,262	(78%)	1,340	(83%)	1,366	(84%)	<0.001	5,035	(78%)
Thiazolidinediones	298	(18%)	389	(24%)	424	(26%)	430	(27%)	<0.001	1,541	(24%)

Parameter	Estimated prescribed insulin dose quartile (units/kg/day)									All identified study patients	
	0.074–0.479		0.480–0.666		0.667–0.913		0.914–3.884		p-value		
DPP-4 inhibitors	51	(3%)	44	(3%)	59	(4%)	47	(3%)	0.442	201	(3%)
GLP1-agonists	12	(1%)	15	(1%)	16	(1%)	22	(1%)	0.351	65	(1%)
Meglitinides	52	(3%)	54	(3%)	54	(3%)	51	(3%)	0.987	211	(3%)
General morbidity:											
Prior large vessel disease, n (%)	491	(30%)	436	(27%)	409	(25%)	411	(25%)	0.004	1,747	(27%)
Prior cancer, n (%)	217	(13%)	221	(14%)	184	(11%)	162	(10%)	0.004	784	(12%)
Prior vision problems, n (%)[d]	617	(38%)	601	(37%)	615	(38%)	608	(37%)	0.914	2,441	(38%)
Prior antihypertensives, n (%)	1116	(69%)	1079	(66%)	1130	(70%)	1135	(70%)	0.102	4,460	(69%)
Prior lipid-lowering drugs, n (%)	927	(57%)	902	(56%)	928	(57%)	952	(59%)	0.343	3,709	(57%)
Prior anti-platelet drugs, n (%)	761	(47%)	760	(47%)	747	(46%)	756	(47%)	0.981	3,024	(47%)
Charlson index, median (IQR)	3.0	(2.0–4.0)	2.0	(1.0–4.0)	2.0	(1.0–4.0)	2.0	(1.0–4.0)	<0.001	2.0	(2.0–4.0)
GP contacts prior year, median (IQR)	15.0	(8.0–25.0)	15.0	(8.0–23.0)	15.0	(9.0-25.0)	15.0	(9.0–25.0)	0.648	15.0	(8.0–25.0)
Insulin regimen[e]:									<0.001		
Basal–bolus	84	(5%)	142	(9%)	190	(12%)	232	(14%)		648	(10%)
Basal	304	(19%)	141	(9%)	115	(7%)	98	(6%)		658	(10%)
Premix	1,031	(64%)	993	(61%)	905	(56%)	791	(49%)		3,720	(57%)
Other or varies[f]	203	(13%)	348	(21%)	406	(25%)	501	(31%)		1,458	(22%)

[a] The nearest record to the index providing it was no more than 365 days before or 30 days after the index date. The search was conducted in the following order: -30 days, +30 days and -365 days.

[b] Nearest recorded status recorded prior to index date.

[c] Time between diabetes presentation date (defined as the date of first recorded diabetes diagnosis or first prescription for a glucose-lowering agent) and the index date.

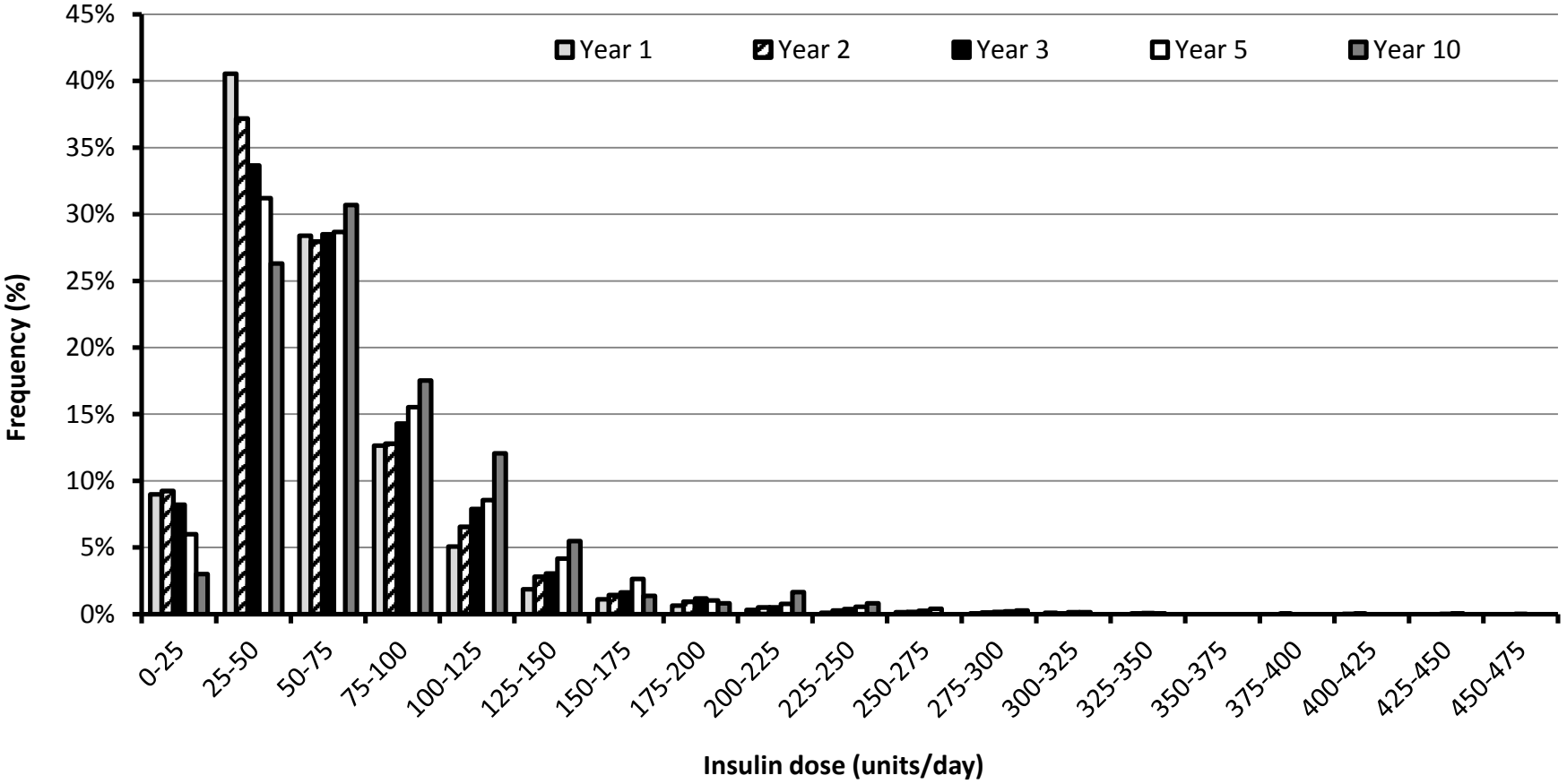
[d] Vision problems include cataracts, glaucoma, retinopathy, maculopathy, macular degeneration, iritis/uveitis, scotoma, papilloedema, nerve palsy, and vision impairments or blindness

[e] During study follow-up.

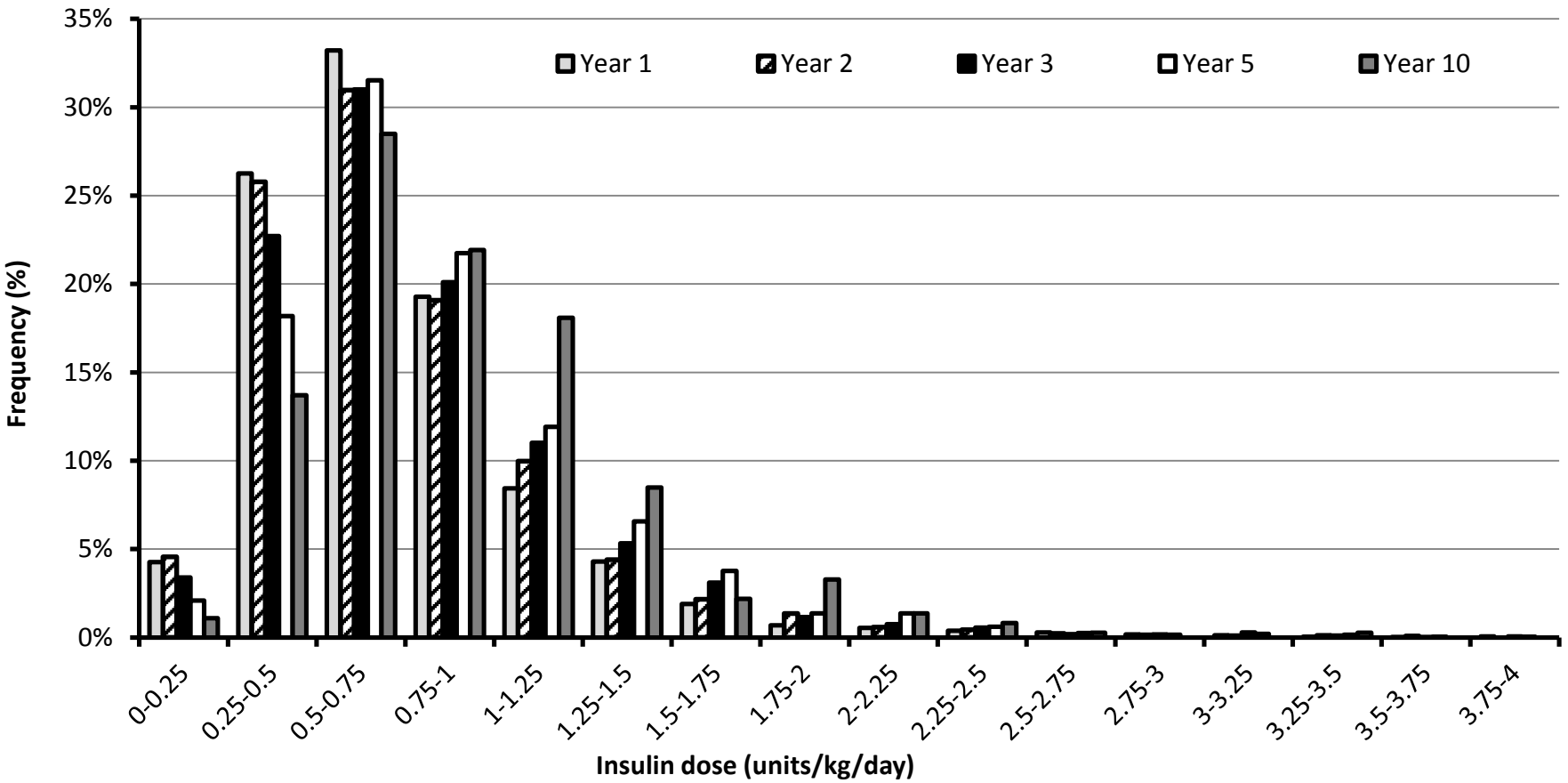
[f] This category also includes people who switch between the three different insulin regimens.

Figure 8.1 Distribution of (a) estimated daily insulin dose and (b) weight-standardised estimated daily insulin dose (units/kg/day) for those who were alive and remained on treatment with insulin monotherapy

a)

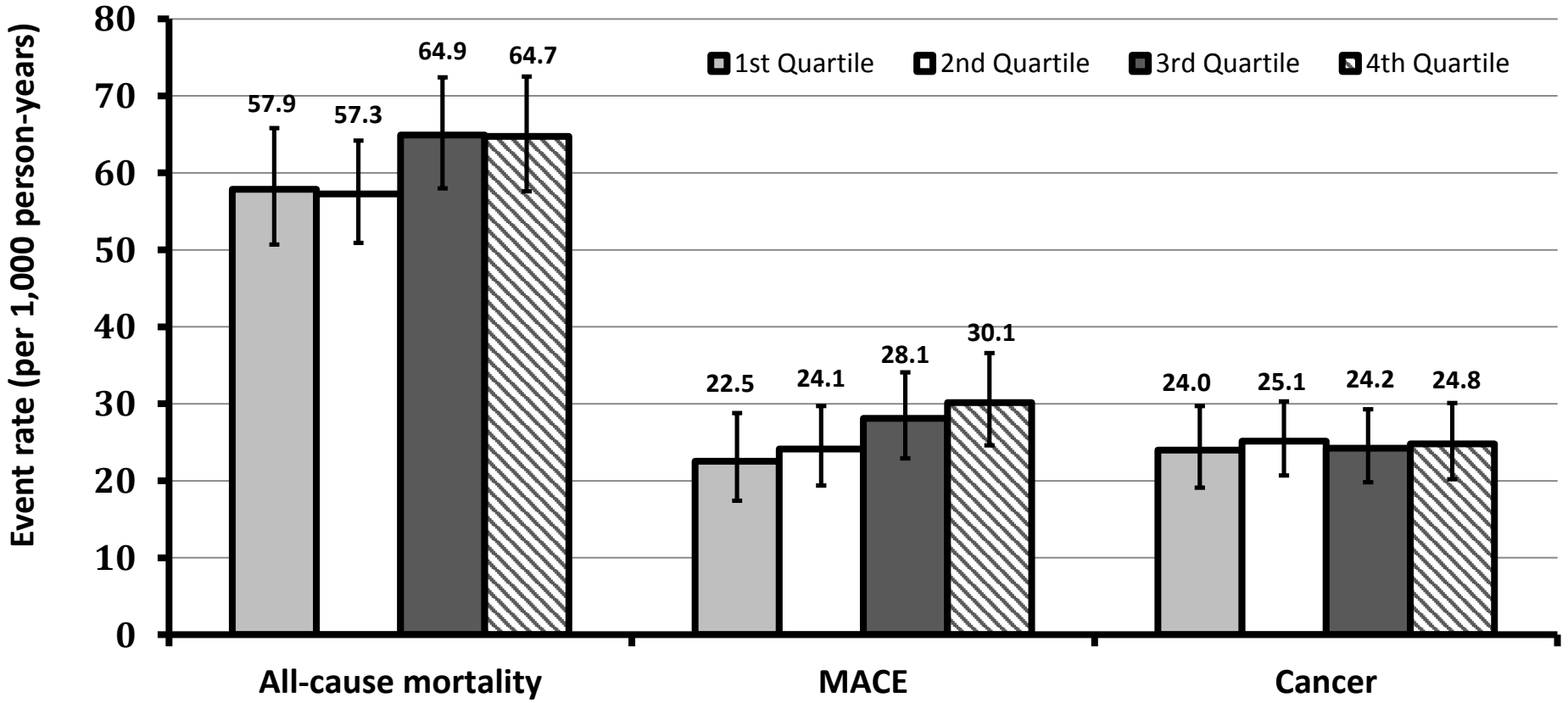


b)



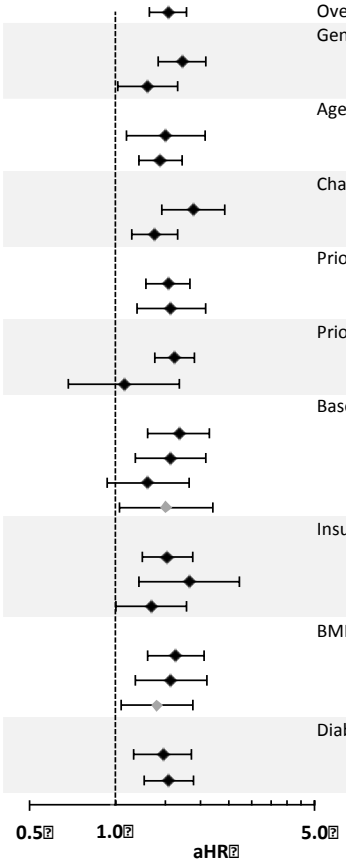
Number of patients included in each year: year 1 = 6,484; year 2 = 5,084; year 3 = 3,566; year 5 = 1,964; year 10 = 365

Figure 8.2 Crude event frequency and event rate per 1,000 person years by average estimated insulin dose quartile in the first year following index date*



*1st insulin dose quartile = 0.074–0.479 units/kg/day, 2nd quartile = 0.480–0.666 units/kg/day, 3rd quartile = 0.667–0.913 units/kg/day, 4th quartile = 0.914–3.884 units/kg/day

Figure 8.3 Adjusted hazard ratios for the association between estimated insulin dose and all-cause mortality for all cases and for specific phenotypic subgroups



Subgroup	aHR	95%CI	p-value	n/N	p-value for test of heterogeneity
Overall	1.54	(1.32−1.78)	<0.001	(1,100/6,484)	
Gender					
Male	1.72	(1.41−2.09)	<0.001	(649/3,643)	
Female	1.30	(1.02−1.66)	0.031	(461/2,830)	0.07
Age (years)					
≤65	1.51	(1.10−2.07)	0.011	(250/3,073)	
>66	1.44	(1.22−1.72)	<0.001	(860/3,408)	0.60
Charlson comorbidity index					
≤2	1.88	(1.46−2.42)	<0.001	(357/3,320)	
≥3	1.38	(1.14−1.66)	0.001	(753/3,148)	0.12
Prior large vessel disease					
No	1.53	(1.28−1.84)	<0.001	(707/4,733)	
Yes	1.57	(1.19−2.07)	0.001	(403/1,747)	0.68
Prior cancer					
No	1.61	(1.38−1.90)	<0.001	(908/5,700)	
Yes	1.07	(0.68−1.69)	0.761	(202/783)	0.15
Baseline HbA1c (%)					
≤8.5	1.67	(1.30−2.15)	<0.001	(370/1,884)	
>8.5 and ≤10.5	1.56	(1.17−2.09)	0.003	(318/1,847)	
>10.5	1.30	(0.93−1.81)	0.122	(276/1,725)	
missing	1.51	(1.03−2.20)	0.033	(146/1,012)	0.41
Insulin regimen					
Basal-bolus or premix	1.53	(1.25−1.87)	<0.001	(753/4,368)	
Basal	1.82	(1.21−2.73)	0.004	(124/626)	
Other	1.34	(1.01−1.78)	0.043	(233/1,444)	0.50
BMI (kg/m^2)					
≤28	1.64	(1.30−2.06)	<0.001	(481/2,806)	
>28	1.57	(1.17−2.09)	0.002	(379/2,422)	
Missing	1.40	(1.05−1.87)	0.023	(250/1,244)	0.59
Diabetes duration (years)					
≤6	1.47	(1.16−1.85)	0.001	(382/3,160)	
>6	1.54	(1.26−1.88)	<0.001	(728/3,318)	0.92

Model specification: Charlson index; BMI; age; gender; prior GP contacts; smoking status; HbA_{1c}; serum creatinine; histories of antiplatelet therapy, lipid-lowering therapy, large vessel disease; duration of diabetes; insulin regimen; and index year. Estimated cumulative insulin dose was added as a yearly updated time-dependent covariate. History of prior cancer and prior antihypertensive therapy initially violated the proportional hazards assumption of the Cox model and so were added as Heaviside functions (< and ≥1095 days). The insulin regimen category 'other' includes people who have received more than one of the following regimens: basal, basal-bolus or premix.

Table 8.2 Sensitivity analysis exploring the effect of different estimations of insulin exposure on the aHR for mortality, MACE, and cancer

	All-cause mortality			MACE			Cancer		
Estimated insulin dose covariate and model description	aHR	95% CI	p-value	aHR	95% CI	p-value	aHR	95% CI	p-value
Average insulin dose in year 1 as a continuous covariate	1.43	(1.23-1.66)	0.000	1.245	(0.95-1.64)	0.117	1.260	(1.00-1.63)	0.079
Continuous time-dependent covariate (no Heaviside functions)	1.52	(1.34-1.72)	0.000				1.187	(0.94-1.5)	0.147
Continuous time-dependent covariate (cases with missing values excluded)	1.57	(1.34-1.84)	0.000	1.308	(0.97-1.76)	0.076	1.402	(1.07-1.83)	0.013
Continuous time-dependent covariate	1.52	(1.34-1.73)	0.000	1.233	(0.97-1.57)	0.089	1.189	(0.94-1.5)	0.143
Time-dependent insulin dose group (units/kg/day)[a]									
<=0.5	1								
>0.5 and <=1.0	0.90	(0.78-1.04)	0.167						
>1.0 and <=1.5	1.19	(0.99-1.44)	0.067						
>1.5	1.90	(1.50-2.40)	0.000						
Time-dependent insulin dose quartile (units/kg/day)[a]									
0.066-0.459	1								
0.460-0.637	0.87	(0.73-1.05)	0.145						
0.638-0.878	0.93	(0.78-1.11)	0.405						
0.879-4.000	1.21	(1.02-1.44)	0.027						
Time-dependent lag continuous insulin dose (year-1)	1.44	(1.25-1.65)	0.000	1.394	(1.09-1.79)	0.008	1.376	(1.09-1.74)	0.008
Time-dependent cumulative continuous insulin dose	1.54	(1.32-1.78)	0.000	1.374	(1.05-1.81)	0.023	1.350	(1.04-1.75)	0.024
Time-dependent continuous insulin dose (last year adjusted)	1.19	(1.02-1.37)	0.022	1.145	(0.89-1.48)	0.302	1.132	(0.89-1.45)	0.321
Time-dependent quartile of insulin dose (last year adjusted) (units/kg/day)[ab]									
0.066-0.459	1								
0.460-0.637	0.70	(0.59-0.83)	0.000						
0.638-0.878	0.74	(0.63-0.87)	0.000						
0.879-4.000	0.75	(0.64-0.89)	0.001						
Average continuous insulin dose in year 1, endpoint = end of data or event[c]	1.28	(1.15–1.43)	<0.001						

[a] Only provided for all-cause mortality endpoint where there was evidence of a non-linear relationship between estimated insulin dose and endpoint (tested by adding the squared dose as a yearly time-updated covariate into the model in addition to the original yearly time-updated insulin dose covariate).
[b] Proportional hazards assumption was violated for estimated insulin dose.
[c] Patients were followed to end of data or death (regimen change of insulin cessation was not used as an endpoint).

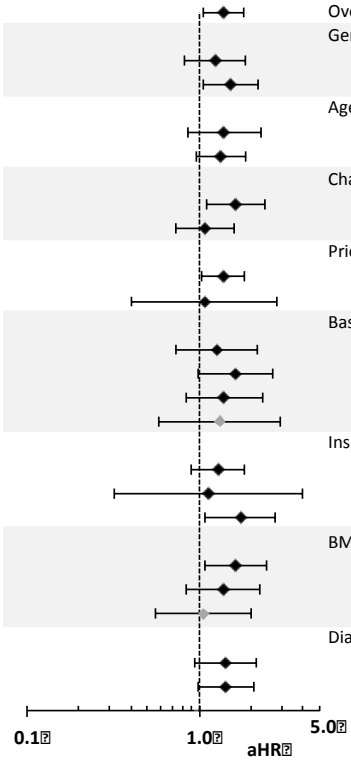
8.3.5. Risk of incident major adverse cardiovascular events

The association between estimated insulin dose and the risk of MACE was not so clear (Figure 8.4). The aHR for estimated insulin exposure was not lower than unity in any of the 20 subgroups and there was no evidence of a difference in effect of increasing estimated insulin exposure between subgroups (test for heterogeneity: p>0.05 for all subgroups)

8.3.6. Risk of incident cancer

The overall pattern of association with incident cancer was also not as clear as that for all-cause mortality (aHR=1.35, 1.04–1.75, Figure 8.5). An increased aHR for the association between estimated insulin dose and incident cancer was observed for males when compared with females (1.84, 1.35–2.52 versus 0.78, 0.48–1.28, p-value for test of heterogeneity = 0.006): and people with a history of large vessel disease when compared with those without a history of large vessel disease (1.97, 1.20–3.22, versus 1.15, 0.83–1.58, p-value for test of heterogeneity = 0.034).

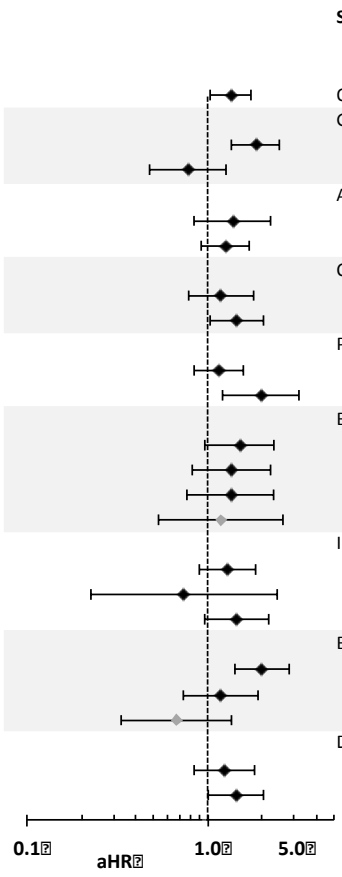
Figure 8.4 Adjusted hazard ratios for the association between estimated insulin dose and MACE for all cases and for specific phenotypic subgroups



Subgroup	aHR	95%CI	p-value	n/N	p-value for test of heterogeneity
Overall	1.37	(1.05–1.81)	0.023	342/4,657	
Gender					
Male	1.23	(0.82–1.85)	0.327	177/2,434	
Female	1.53	(1.06–2.21)	0.024	165/2,215	0.34
Age (years)					
≤65	1.40	(0.86–2.28)	0.178	115/2,533	
>66	1.33	(0.96–1.85)	0.085	227/2,123	0.85
Charlson comorbidity index					
≤2	1.63	(1.10–2.40)	0.014	173/2,879	
≥3	1.08	(0.73–1.60)	0.697	169/1,713	0.41
Prior cancer					
No	1.38	(1.04–1.83)	0.027	304/4,093	
Yes	1.07	(0.41–2.82)	0.892	38/542	0.73
Baseline HbA1c (%)					
≤8.5	1.26	(0.73–2.17)	0.409	89/1,121	
>8.5 and ≤10.5	1.61	(0.98–2.66)	0.061	102/1,369	
>10.5	1.40	(0.84–2.33)	0.195	105/1,360	
missing	1.32	(0.58–2.97)	0.506	46/733	0.68
Insulin regimen					
Basal-bolus or premix	1.29	(0.90–1.84)	0.168	234/3,066	
Basal	1.14	(0.32–4.01)	0.841	22/378	
Other	1.74	(1.08–2.78)	0.022	86/1,135	0.60
BMI (kg/m^2)					
≤28	1.62	(1.07–2.45)	0.023	135/2,028	
>28	1.38	(0.84–2.24)	0.200	140/1,711	
Missing	1.06	(0.56–2.01)	0.865	67/863	0.93
Diabetes duration (years)					
≤6	1.42	(0.94–2.16)	0.094	126/2,405	
>6	1.42	(0.97–2.07)	0.068	216/2,246	0.56

Model specification: Charlson index; BMI; age; gender; prior GP contacts; smoking status; HbA_{1c}; serum creatinine; histories of antiplatelet therapy, lipid-lowering therapy, antihypertensive therapy, cancer, large vessel disease; duration of diabetes; insulin regimen; and index year. Estimated cumulative insulin dose was added as a yearly updated time-dependent covariate. The insulin regimen category 'other' includes people who have received more than one of the following regimens: basal, basal-bolus or premix.

Figure 8.5 Adjusted hazard ratios for the association between estimated insulin dose and incident cancer for all cases and for specific phenotypic subgroups.



Subgroup	aHR	95%CI	p-value	n/N	p-value for test of heterogeneity
Overall	1.35	(1.04–1.75)	0.024	382/5597	
Gender					
Male	1.84	(1.35–2.52)	<0.001	239/3154	
Female	0.78	(0.48–1.28)	0.326	143/2443	0.006
Age (years)					
≤65	1.38	(0.85–2.24)	0.197	112/2768	
>66	1.25	(0.92–1.71)	0.156	270/2804	0.52
Charlson comorbidity index					
≤2	1.19	(0.79–1.80)	0.395	189/3255	
≥3	1.46	(1.04–2.06)	0.030	193/2332	0.72
Prior large vessel disease					
No	1.15	(0.83–1.58)	0.405	276/4088	
Yes	1.97	(1.20–3.22)	0.007	106/1499	0.03
Baseline HbA1c (%)					
≤8.5	1.50	(0.97–2.33)	0.067	119/1555	
>8.5 and ≤10.5	1.36	(0.83–2.23)	0.224	116/1595	
>10.5	1.34	(0.78–2.32)	0.294	97/1499	
missing	1.19	(0.54–2.63)	0.672	50/888	0.08
Insulin regimen					
Basal-bolus or premix	1.28	(0.89–1.84)	0.183	247/3754	
Basal	0.74	(0.22–2.43)	0.614	32/513	
Other	1.45	(0.97–2.18)	0.072	103/1305	0.60
BMI (kg/m2)					
≤28	1.99	(1.40–2.83)	<0.001	171/2351	
>28	1.18	(0.73–1.92)	0.494	133/2103	
Missing	0.67	(0.33–1.36)	0.272	78/1072	0.67
Diabetes duration (years)					
≤6 years	1.24	(0.83–1.83)	0.295	161/2769	
>6 years	1.43	(1.00–2.05)	0.049	221/2820	0.42

Model specification: Charlson index; BMI; age; prior GP contacts; HbA_{1c}; serum creatinine; histories of antiplatelet therapy, lipid-lowering therapy, antihypertensive therapy, cancer, large vessel disease; duration of diabetes; insulin regimen; and index year. Estimated cumulative insulin dose was added as a yearly updated time-dependent covariate. Smoking status and gender initially violated the proportional hazards assumption of the Cox model and so were added as Heaviside functions (<1095 and ≥1095 days and <730 and ≥730 days, respectively). The insulin regimen category 'other' includes people who have received more than one of the following regimens: basal, basal-bolus or premix

8.4. Discussion

Adding to recent observational data that report an association between people with type 2 diabetes treated with insulin and the risk of adverse outcomes,[60] here we found that there was an association between the estimated dose of prescribed insulin exposure and increased risk of all-cause mortality. A statistically significant association with MACE and cancer was also observed. The patterns of association were generally consistent in relevant phenotypic subgroups. This finding was resonant with previous findings.[60]

One possible explanation for our findings is that exposure to higher insulin doses could have harmful effects. Insulin resistance and hyperinsulinaemia are thought to increase basal insulin signalling, which in turn contributes to insulin resistance and atherosclerosis.[182] Meta-analyses have suggested that hyperinsulinaemia is a weak risk indicator for cardiovascular disease.[179] In addition, hyperinsulinaemia can lead to tumour growth.[514] In comparison with endogenous insulin secretion, injection of exogenous insulin may result in the exposure of peripheral tissues to a higher concentration of insulin.[516] However, conversely, a study using streptozotocin-diabetic rats has shown that peripheral insulin delivery can lead to adequate glucose control without inducing hyperinsulinaemia.[184]

Hypoglycaemia, a common side effect of injected insulin, has been shown to prolong the QT interval and cause Ca^{2+} overload, leading to malignant ventricular arrhythmias, an effect thought to be greatest in people with pre-existing diabetes and cardiovascular disease.[76,195] Stahn and colleagues have recently found that people with type 2 diabetes and a prior history of cardiovascular disease treated with insulin and/or sulfonylureas experienced a high incidence of asymptomatic severe episodes of

hypoglycaemia and silent severe arrhythmias.[198] A recent study documented that patients who received insulin doses of ≥0.6 units/kg were at increased odds of hypoglycaemia.[199] After multifactorial adjustment, the higher odds of hypoglycaemia with increasing insulin doses remained (0.6–0.8 units/kg: OR 2.10 [95% CI 1.08–4.09], p=0.028; 0.8 units/kg: 2.95 [1.54–5.65], p=0.001). In contrast, the adjusted odds of hypoglycaemia were no higher in patients who received only 0.2–0.6 units/kg. In the ORIGIN study,[80] severe hypoglycaemia occurred significantly more often in patients randomised to insulin glargine compared with those in the control arm, despite the low insulin requirement (6.3% vs. 1.8%; p<0.001). Remarkably, in a very recent report from the ORIGIN trial,[200] severe hypoglycaemia was associated with a greater risk of mortality (aHR=1.74, 95% CI 1.39–2.19, p<0.001), cardiovascular death (1.71, 1.27–2.30, p<0.001), and arrhythmia-related death (1.77, 1.17–2.67, p=0.007). However, the severe hypoglycaemia hazard for all outcomes was higher with standard care than with regimens that included low-dose insulin glargine.

Links between injected insulin and the three outcomes investigated here have been reported previously, but importantly, very few RCTs have compared insulin-based, glucose-lowering regimens with other glucose-lowering regimens. The ORIGIN study compared insulin glargine with standard treatment in people with type 2 diabetes and found that insulin glargine had a no statistically significant impact on cardiovascular outcomes and cancers.[80] This result appears to conflict with our findings; however, it is important to note that the patients included in the ORIGIN study had type 2 diabetes treated with no more than one glucose-lowering therapy or had IGT or IFG.[80] The insulin dose was relatively low after six years (0.40 units per kg; IQR, 0.27 to 0.56). In addition, 65% of the insulin glargine group were also using other glucose-lowering

agents (46.5% combined glargine with metformin) and 11% of the standard care group were using insulin.[80] In the UKPDS, patients treated with insulin experienced a sustained increase in plasma insulin levels.[67] Despite this, an excess of macrovascular outcomes was not observed in the intensively treated arm.[67] In addition, patients treated with insulin were not more at risk of myocardial infarction.[67] However, the UKPDS was not specifically designed to assess the safety of insulin in type 2 diabetes. Observational studies have shown that insulin treatment was associated with an increased risk of cardiovascular events (2.5-fold)[223] and of MIs, and that risk increased with increasing insulin exposure.[251] During the follow-up to the DIGAMI 2 study, insulin was associated with a statistically significant increase in non-fatal cardiac events.[248] However, there were some limitations to the original study where less than half the number of planned participants were recruited to the study and FPG levels were above target and similar in the three study groups.[247] Patients using exogenous insulin have increased risk of cancer-related mortality in comparison with metformin[277] and other therapies,[278] and there is a graded association between insulin exposure and death from cancer has been reported.[279] A recent systematic review and meta-analysis concluded that the use of exogenous insulin is associated with several types of cancer.[517] In terms of all-cause mortality, insulin-based treatment has been associated with a higher risk of mortality when compared with combination therapies of oral glucose-lowering medications (aHR=1.5, 1.4–1.6) [60]. In a retrospective observational study based in Denmark, Mogensen and colleagues found that insulin was associated with a significantly increased risk of all-cause mortality when compared with metformin plus sulfonylurea, DPP-4 inhibitors, and GLP-1 agonists, and with a significantly increased risk of cardiovascular mortality when compared with metformin plus sulfonylurea or DPP-4 inhibitors [518]. In addition, a graded association has been

found between insulin exposure and mortality.[255] In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), a significant association was found between exogenous insulin exposure and all-cause and ischaemic mortality after adjusting for age and sex (HR 1.70, 95% CI 1.23–2.34 per unit/kg/day increase) but this association became non-significant following multivariate adjustment (1.20, 0.85–1.69).[519]

One of the main criticisms of this type of observational study is the possibility of confounding by indication, where the glucose-lowering regimen prescribed is not independent of the severity of the disease or phenotype. In addition, the outcome may be dependent upon other factors that are either unknown or cannot be fully adjusted for in the statistical modelling. The effect has been here minimised by our selecting only those patients initiated on insulin monotherapy. However, this study is complicated in that increasing insulin dose could be a measure of diabetes deterioration. Duration of diagnosed diabetes was used as a potential covariate in the Cox proportional hazards model, although true diabetes duration could not be determined as the length of time diabetes remained undiagnosed is not quantifiable. Epidemiological analysis of the CRPD data does not allow us to answer the clinically relevant question of why some patients received large amounts of insulin that translated into high estimated daily doses of insulin (>1.5 units/kg/day). We cannot exclude the possibility that these patients had a particularly high degree of insulin resistance on starting their insulin therapy. Insulin resistance is known to be a strong predictor of macrovascular complications including coronary heart disease and stroke [520,521]. However, obesity is linked to insulin resistance [522] and mean BMI was similar across the four dose groups (Table 8.1). It is plausible that this confounding by indication may not have been fully accounted for within the Cox proportional hazards

model. However, with the exception of large vessel disease and sex subgroups for the cancer endpoint, the results remained consistent across a wide range of subgroup analyses. Wastage of insulin may have led to an overestimation of insulin dose, particularly for patients whose insulin dose is within the highest insulin dose quartile. Insulin exposure was calculated from the volume of insulin prescribed. We were unable to determine from the data whether the patient collected or used all the insulin prescribed to them. A larger proportion of patients in the high dose insulin groups switched between basal-bolus, premix or basal insulin regimens (31% versus 13% in the highest and lowest insulin dose quartiles). At each switch, a certain amount of insulin is likely to be wasted leading to an overestimation of their insulin dose. Patients who switch may also be the least well-controlled. When quartiles of estimated insulin dose were added to the Cox proportional hazards model, the highest mortality effect was seen in the top quartile of estimated insulin dose (2nd quartile = 0.90, 95% CI 0.78–1.04; 3rd quartile = 1.19, 0.99–1.44; 3rd quartile = 1.90 1.50–2.40).

Irrespective of the causality between high insulin dose and mortality, attempts to reduce the insulin dosage by the concomitant use of other drugs such as metformin, pioglitazone, GLP-receptor agonists, or SGLT2 inhibitors could be considered.

8.4.1. Study limitations

CPRD contains data collected from routine practice, therefore some data may be missing and coding imperfections may lead to the misclassification of diabetes type. However, only those patient records meeting CPRD's own research-quality criteria were included in this study, and rules were applied to maintain consistency in the selection of patients with type 2 diabetes. Insulin doses in type 1 and latent

autoimmune diabetes of adulthood (LADA) may be lower than those prescribed in type 2 diabetes, which is characterised by insulin resistance. Therefore, there is a possibility that the association between estimated insulin dose and adverse outcomes could be explained by the increased risk of adverse outcome in people with type 2 diabetes compared with those with type 1 diabetes or LADA. However, the Collaborative Atorvastatin Diabetes Study (CARDS) found that vascular complications were similar in patients with LADA or type 2 diabetes [523]. This is contrary to the hypothesis that the lower risk of MACE may be explained by the inadvertent inclusion of LADA patients in our study.

The site of initiation of insulin (primary or secondary care) has not been investigated. People who initiate in hospital may have more comorbidities than those who start insulin in primary care and may receive different dose titration. In addition, patients initiating insulin as monotherapy may have more co-morbidities (for example cardiac or renal disease) compared with patients adding insulin to existing glucose-lowering therapy, for example metformin. In this study, the percentage of people with a history of large vessel disease was relatively high. Average baseline creatinine levels were also relatively high. In addition, a high proportion of subjects had previously received other glucose-lowering agents, which had been stopped prior to the initiation of insulin. The reasons for this cannot be deduced from the data. Although there is no reason to suggest that these patients are not reflective of people who initiate insulin monotherapy in the general population, this may affect the generalisability of the results.

Retrospective observational studies can only demonstrate possible associations with events; prospective RCTs are required to establish causality. However, retrospective

observational studies are considerably cheaper to carry out than large RCTs whilst still achieving large sample sizes.

Insulin dose is rarely recorded in CPRD. Therefore, exposure was estimated using the total number of international units prescribed per year to generate an average weight-standardised daily dose. There were some limitations to the methods used to estimate the number of units of insulin prescribed (Appendix 2). Although we used a consistent approach throughout, the rules applied might have led to an under- or overestimation of the prescribed number of international units. These limitations are likely to have introduced noise into the analysis that would have disguised any underlying patterns of association.

Insulin detemir is less potent than other insulins. The concentration of the proprietary formulation of insulin detemir is four times that of other insulins (2,400 compared with 600 nmol/ml) so that the volume of insulin detemir administered is equivalent to other insulin products. Although this seems to be the case for type 1 diabetes, in type 2 diabetes, higher volumes of insulin detemir may need to be administered in order to produce the same glucose-lowering effect as equivalent insulin products [524]. A sensitivity analysis was therefore carried out. The aHR for patients who received at least one detemir prescription (N=617) was 1.58 (95% CI 0.81–3.06; p=0.177). For those patients who did not receive at least one prescription for insulin detemir during the study period (N=5,867), the aHR for estimated insulin dose was 1.54 (1.32–1.81).

We assumed that there was a direct association between the amount of insulin prescribed and the amount injected. The presence of a prescription record in CPRD can only indicate that insulin was prescribed: we could not determine whether the patient collected that prescription from the pharmacy or whether they used all of the insulin.

The assumption that patients will use their whole insulin supply before they reorder their next prescription is also likely to be unrealistic. Patients may waste some of their insulin. Prescriptions for insulin may not be regularly collected every 28 days as is common for oral medication. Therefore, in order to gauge how long a patient's last prescription for insulin would last, it was necessary to use the time between a patient's last and penultimate prescription.

Patient follow-up was relatively short (an average of 3.3 years). This may be shorter than the period of time that some conditions need to develop (e.g. some cancers), which may have been influenced by previous glucose-lowering regimens. However, no one has postulated that insulin causes cancer—the thesis is that insulin has growth-promoting effects, which would be observed as a change in the rate of cancer detection. Furthermore, MACE and death are acute events.

Insulin dose was estimated using various methods before adding it into the Cox proportional hazard model (Table 8.2) and similar results were produced. However, for all-cause mortality, the relationship between insulin dose and the endpoint did not seem to be linear when insulin exposure was modelled as an annual, average, weight-standardised dose. Possible explanations for this finding could include hospitalisation prior to an event, leading to a reduction in the ordering of insulin prescriptions in primary care. However, as a sensitivity analysis, quartiles of average, yearly-updated insulin dose were added to the Cox model and the second and third quartiles were not significantly different from the first insulin dose quartile. Only the fourth quartile was associated with a significantly higher aHR. However, categorising a continuous covariate may have led to some loss of power. The number of people included in some

of the subgroup analyses was small and in these cases over-fitting of the model may have occurred.

8.4.2. Conclusion

Any potential risks associated with insulin therapy need to be seen in the context of its potential to lower blood glucose, where achieving adequate glucose control is important in reducing the risk of microvascular events in particular.[67] However, insulin replacement therapy in type 2 diabetes is now common, whereas it was relatively uncommon 20 years ago.[422]

Here we have demonstrated a dose association between exogenous insulin and all-cause mortality, MACE and cancer in people with type 2 diabetes. Limitations associated with both the estimation of insulin dose and also the retrospective observational nature of the study mean that this hypothesis should be tested using an interventional study design. Further research is now needed to investigate the risks and benefits of exogenous insulin in people with type 2 diabetes. These findings are in agreement with previously published studies reporting associations between insulin use in type 2 diabetes and serious adverse outcomes[60,223,248,251,255,277–279,517,518] but contrary to findings from ORIGIN.[80]

9. Impact of concomitant metformin on insulin-treated type 2 diabetes

9.1. Introduction

9.1.1. Background

The rate of insulin use in type 2 diabetes increased more than six-fold in the UK between 1991 and 2010.[422] In 1991, almost all patients with type 2 diabetes used insulin as monotherapy.[422] By 2010, 42% of these patients were prescribed insulin in combination with metformin; the percentage treated with insulin monotherapy decreased to 37%.[422] The USA has also seen a trend towards increased prescribing of insulin in combination with oral hypoglycaemic agents.[467] A Cochrane review reported that bedtime NPH insulin in combination with oral hypoglycaemic agents provided comparable glycaemic control to insulin monotherapy but with generally lower doses of insulin.[83] A position statement of the ADA and the EASD recommends that metformin therapy be continued when insulin is initiated.[7]

A possible association between increasing estimated insulin dose and increased all-cause mortality in people with type 2 diabetes treated with insulin monotherapy has been reported.[525] Previous data have also demonstrated a direct association between insulin exposure and mortality.[255] A recent article published in JAMA by Roumie et al found that the addition of insulin to existing metformin treatment was associated with an increased risk of cardiovascular events and all-cause mortality versus the addition of sulfonylurea in people with type 2 diabetes.[346] We recently reported that people with type 2 diabetes using insulin were at an increased risk of a combined endpoint defined as first MACE, first cancer, or mortality, with the risk being significantly higher

for users of insulin monotherapy compared with users of insulin plus concomitant metformin.[61] However, this study did not account for insulin exposure. In addition to its potential for lowering concomitant insulin dose,[83] metformin may protect against cancer through AMP dependent and independent mechanisms,[81] improve endothelial dysfunction,[296–298] body weight, lipids and blood pressure[299,300] and has been shown to reduce plasminogen activated inhibitor-1, a risk factor for cardiovascular disease.[301] Relative to the use of insulin alone, the use of metformin in combination with insulin has been associated with a reduced risk of cardiovascular events, cancer and death from any cause.[61,62,345]

9.1.2. Aims and objectives

The aim of this study was to determine if combining insulin with metformin reduced the risk of adverse outcome compared with insulin monotherapy, taking insulin dose into account.

9.2. Methods

9.2.1. Data source

The data source was the CPRD,[427] a longitudinal database collating pseudonymised data collected in a non-interventional way from 660 participating primary-care practices throughout the UK. CPRD is representative of the UK population and contains 13 million patients and approximately five million are actively registered and can be followed prospectively. CPRD is linked to hospital data. Data were from January 2000 to January 2013. Approval for this study was granted by the CPRD ISAC (reference number 11_017).

9.2.2. Patients

Patients were included if they had more than one diagnosis exclusively for type 2 diabetes, or prescriptions for at least two differing classes of glucose-lowering medication other than insulin, or at least one diagnosis for type 2 diabetes plus prescriptions for at least one glucose-lowering medication excluding insulin. Patients were included only if they initiated a regimen of insulin monotherapy or insulin in combination with metformin. The study index date was defined as the date of first insulin prescription, with a wash-in period of ≥365 days.

Patients were excluded if they had any record for secondary diabetes, an estimated yearly average insulin dose greater than 4 units/kg/day, insulin prescribed on only one occasion, or no recorded weight. Patients with a prior history of large vessel disease or cancer were excluded from analyses in which MACE or cancer were the respective endpoints. Only patients with at least two prescriptions for insulin were included as

this was a requirement for the calculation of daily dose. In order to avoid an immortal time bias due to the exclusion of people with only one prescription for insulin (thereby ensuring that no patients could die before their second insulin prescription), only those patients with at least 180 days' follow-up were included in the study. A gap of more than 180 days between prescriptions was used as an indicator of treatment discontinuation.

In order to determine whether patients prescribed insulin plus metformin were at a greater risk of all-cause mortality than patients prescribed alternative glucose-lowering regimens, we also compared patients treated with insulin plus metformin and insulin monotherapy with a reference group of subjects treated with metformin plus sulfonylurea combination therapy. The selection criteria for the metformin and Sulfonylurea cohort have been described previously.[61] For this comparison only, any patients included in more than one therapy group were excluded from the analysis in order to prevent immortal time bias.

9.2.3. Study endpoints

The primary outcome was all-cause mortality, with a secondary endpoint of the first of incident MACE (defined as incident myocardial infarction, stroke, angina, and or coronary revascularisation), incident cancer (excluding non-melanoma skin cancer), or death. The censor date was defined as the earliest of: the end of a patient's recorded data, 90 days after their date of transfer to an alternative glucose-lowering, or their last prescription for insulin.

9.2.4. Estimation of insulin dose

Weight-standardized daily insulin exposure (units/kg/day) was estimated from the volume of insulin prescribed. For each insulin prescription, the quantity was converted to the number of international units prescribed and divided by the nearest recorded weight measurement. The cumulative average insulin dose was calculated on an annualized basis.

9.2.5. Statistical methods

Time to each endpoint was evaluated using Cox proportional hazards modelling. Time zero for the Cox model and the calculation of the crude event rates was taken as the first prescription for insulin plus 180 days. People with events (cancer or MACE) prior to this date were excluded from the relevant analysis. The following baseline covariates were identified *a priori* and included in the Cox proportional hazards model as continuous covariates: age, serum creatinine, BMI, duration of diabetes, index year, Charlson comorbidity index,[374] and the number of GP contacts in the year prior to index date. Metformin exposure, HbA_{1c}, gender, insulin regimen, history of cancer or large vessel disease, smoking status, and prior exposure to lipid-lowering, anti-platelet, and antihypertensive therapies were included as categorical variables. Missing baseline values were imputed using multiple imputation for serum creatinine, HbA_{1c}, and BMI.

Cumulative weight-standardized insulin exposure was estimated for each subsequent year following insulin initiation and analysed as a time-dependent variable,[255] selected because of the postulated mechanism by which prolonged hyperinsulinaemia is related

to cancer[514] and cardiovascular morbidity.[182,515] In addition, cumulative insulin exposure is less sensitive to changes in prescriptions patterns. Other measures of insulin exposure were evaluated in sensitivity analysis.

aHRs were calculated with 95% confidence intervals. The proportional hazards assumption was tested by examining the Pearson correlation between Schoenfeld residuals and the rank of survival time for cases that had progressed to death. Where appropriate, interactions with time were used to assess the proportional hazards assumption. A test of heterogeneity between subgroups was conducted for each subgroup analysis using interactions between the subgroup covariate and study arm.

Baseline characteristics were compared using the chi-squared test for categorical variables and one-way ANOVA or Kruskal–Wallis test for continuous variables, depending on their distribution. Levene's test was employed to test for homogeneity of variances. If the assumption of homogeneity of variances was violated, Welch's F was used.

Patients prescribed insulin monotherapy were matched to patients prescribed insulin plus metformin by propensity score, incorporating age, gender, year of index exposure, diabetes duration, BMI, serum creatinine, GP contacts in the 12 months to index date, HbA_{1c}, Charlson index, smoking status, history of prior cancer, history of prior large vessel disease, prior exposure to antihypertensives, lipid-lowering therapy or antiplatelet therapy and line of therapy. Only patients with complete (i.e. non-imputed) data for the matching criteria were considered for matching. Propensity matching was carried out using IBM SPSS Statistics 20 using the SPSS R Essentials plug-in. Logistic regression was used to generate the propensity score. Nearest neighbour

1:1 matching was implemented and the caliper was set at 0.1 of the standard deviation of the logit of the propensity score.

9.3. Results

We identified 12,020 subjects with type 2 diabetes who progressed to insulin treatment as monotherapy or in combination with metformin (Table 9.1). Of these, 5,536 were prescribed insulin plus metformin and 6,484 were prescribed insulin monotherapy. Subjects were followed up for an average of 3.5 (median 2.5) years; a total follow-up of 41,747 years.

9.3.1. Baseline characteristics

Baseline characteristics by regimen are detailed in Table 9.1, separating the insulin into lower and higher estimated doses at the median across both groups. Patients treated with insulin plus metformin were younger than those treated with insulin monotherapy (60.0 years versus 64.3 years, $p<0.001$). People in the insulin plus metformin group had higher mean BMI (31.2kg/m^2 versus 28.2kg/m^2 for insulin plus metformin and insulin monotherapy, respectively, $p<0.001$) and lower median serum creatinine levels (83.0 versus 95.0 µmol/l, $p<0.001$). More patients receiving insulin monotherapy had a history of large vessel disease (27% versus 14% for insulin monotherapy and insulin plus metformin, respectively, $p<0.001$) and cancer (12% versus 8%, $p<0.001$). The baseline characteristics for propensity matched patients are detailed in Table 9.2.

Table 9.1 Baseline characteristics by first exposure to each selected glucose-lowering regimen and average estimated insulin dose[a] over the study period

Parameter	Insulin monotherapy				Insulin plus metformin				Metformin plus sulfonylurea		*p*-value
	Lower Dose		Higher Dose		Lower Dose		Higher Dose				
Number of people, n (%)	3,087	(10)	3,397	(10)	2,922	(9)	2,614	(8)	20,346	(63)	
Males, n (%)	1,845	(60)	1,798	(53)	1,682	(58)	1,504	(58)	12,234	(60)	<0.001
Age at index, mean (median), years	64.8	(67.0)	63.8	(66.0)	60.4	(62.0)	59.5	(60.0)	62.4	(63.0)	<0.001
HbA_{1c}, mean (SD), %	9.4	(2.2)	9.9	(2.2)	9.9	(1.9)	10.1	(1.7)	8.9	(1.8)	<0.001
Systolic blood pressure, mean (SD), mmHg	135	(20)	136	(20)	137	(17)	137	(17)	138	(17)	<0.001
Smoking status:											<0.001
Non-smoker, n (%)	1,156	(37)	1,393	(41)	1,104	(38)	987	(38)	7,744	(38)	
Ex-smoker, n (%)	1,303	(42)	1,344	(40)	1,238	(42)	1,133	(42)	9,153	(45)	
Current smoker, n (%)	628	(20)	660	(19)	580	(20)	494	(19)	3,449	(17)	
Total cholesterol , mean (SD), mmol/l	4.7	(1.2)	4.7	(1.2)	4.6	(1.1)	4.6	(1.1)	4.6	(1.2)	<0.001
Serum creatinine, median (IQR), µmol/l	97	(77–132)	93	(76–123)	83	(71–98)	83	(71–97)	85	(74–98)	<0.001
Diabetes duration, median (IQR), years	5.7	(1.8–10.7)	6.7	(2.7–11.5)	6.8	(3.3–10.8)	7.0	(4.1–11.1)	2.8	(1.1–5.2)	<0.001
BMI, mean (SD), kg/m^2	28.4	(5.9)	28.1	(5.9)	31.1	(6.0)	31.4	(5.8)	31.2	(6.2)	<0.001
General morbidity:											
Prior large vessel disease, n (%)	887	(29)	860	(25)	441	(15)	353	(14)	2,498	(12)	<0.001
Prior cancer, n (%)	410	(13)	374	(11)	234	(8)	201	(8)	1,619	(8)	<0.001
Prior antihypertensives, n (%)	2,083	(67)	2,377	(70)	2,027	(69)	1,920	(73)	14,720	(72)	<0.001
Prior lipid-lowering drugs, n (%)	1,744	(56)	1,965	(58)	2,032	(70)	1,876	(72)	13,314	(65)	<0.001
Prior anti-platelet drugs, n (%)	1,448	(47)	1,576	(46)	1,387	(47)	1,289	(49)	10,048	(49)	0.002
Charlson morbidity index, median (IQR)	2	(1–4)	2	(1–4)	2	(1–3)	2	(1–3)	1	(1–2)	<0.001

Parameter	Insulin monotherapy				Insulin plus metformin				Metformin plus sulfonylurea		*p*-value
	Lower Dose		Higher Dose		Lower Dose		Higher Dose				
GP contacts prior year, median (IQR)	15	(8–24)	15	(9–25)	13	(7–21)	13	(8–22)	9	(5–15)	<0.001
Insulin regimen:											<0.001
Basal–bolus, n (%)	216	(7)	432	(7)	264	(9)	436	(17)	–		
Basal, n (%)	436	(14)	222	(7)	869	(30)	361	(14)	–		
Premix, n (%)	1,926	(62)	1,794	(53)	1,372	(47)	1,120	(43)	–		
Other or varies, n (%)	509	(16)	949	(28)	417	(14)	697	(27)	–		

[a] Lower-dose insulin: ≤0.648units/kg/day; higher-dose insulin: >0.6480units/kg/day (where the median insulin dose =0.648 units/kg/day). When comparing metformin plus sulfonylurea with the two insulin regimens in the Cox proportional hazards model, duplicate cases were removed. These duplicates have been excluded from the baseline characteristics for the metformin plus sulfonylurea group but not for the two insulin regimens. This is because these duplicate cases are included in the analyses comparing the two insulin regimens only.

Table 9.2 Baseline Characteristics for propensity matched patients

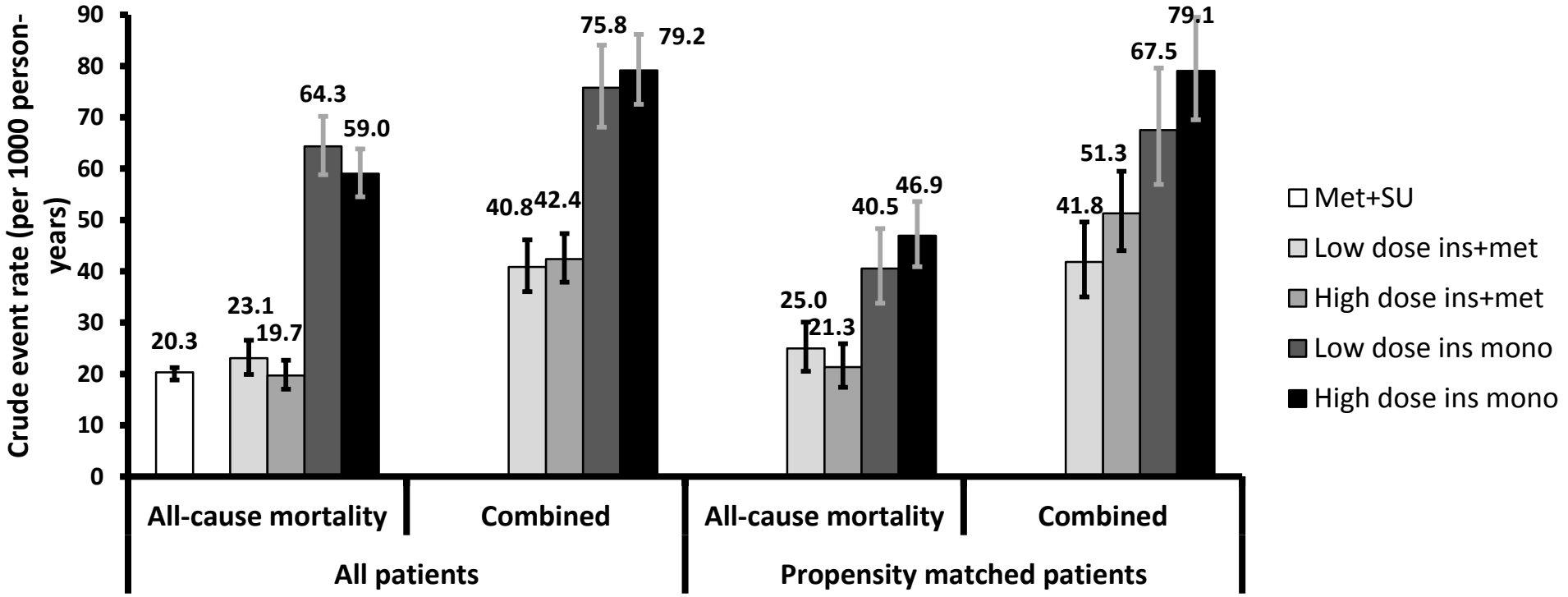
Parameter	Insulin monotherapy		Insulin plus metformin		*p*-value
Number of people, n (%)	2,757	(50%)	2,757	(50%)	
Males, n (%)	1,584	(57%)	1,564	(57%)	0.586
Age at index, mean (median), years	61.9	(63.0)	61.8	(63.0)	0.066
HbA_{1c}, mean (SD), %	9.9	(2.2)	9.9	(1.8)	0.776
Systolic blood pressure, mean (SD), mmHg	134.7	(18.4)	136	(17.5)	0.013
Smoking status:					0.084
Non-smoker, n (%)	1,043	(38%)	1,007	(37%)	
Ex-smoker, n (%)	1,153	(42%)	1,232	(45%)	
Current smoker, n (%)	561	(20%)	518	(19%)	
Total cholesterol, mean (SD), mmol/l	4.7	(1.2)	4.6	(1.1)	<0.001
Serum creatinine, median (IQR), µmol/l	86	(72.0–103.0)	87	(74.0–103.0)	0.062
Diabetes duration, median (IQR), years	6.2	(2.6–11.0)	6.8	(3.6–10.9)	<0.001
BMI, mean (SD), kg/m^2	29.2	(6.1)	29.7	(5.5)	
General morbidity:					
Prior large vessel disease, n (%)	524	(19%)	502	(18%)	0.446
Prior cancer, n (%)	285	(10%)	266	(10%)	0.394
Prior antihypertensive, n (%)	1,916	(69%)	1,932	(70%)	0.639
Prior lipid-lowering drugs, n (%)	1,874	(68%)	1,906	(69%)	0.353
Prior anti-platelet drugs, n (%)	1,303	(47%)	1,306	(47%)	0.936
Charlson morbidity index, median (IQR)	2	(1.0–3.0)	2	(1.0–3.0)	0.515
GP contacts prior year, median (IQR)	15	(9–24)	14	(8–24)	0.130

9.3.2. Crude event rates

There were 1,486 deaths amongst patients using any insulin regimen, a rate of 41.5 (95% CI 39.4–43.6) deaths per 1,000 person-years. After excluding people with prior cancer and MACE, 1,428 patients experienced the combined endpoint, a rate of 58.1 (55.1–61.1) events per 1,000 person-years. Crude event rates were highest for insulin monotherapy for both all-cause mortality and the combined endpoint. Patients in the higher estimated insulin dose groups for both insulin regimens were associated with an increased crude event rate for the combined endpoint but a decreased crude event rate for all-cause mortality (Figure 9.1).

For the propensity matched patients, there were 534 deaths and 674 combined events. The corresponding event rates were 32.8 (30.1–35.7) and 59.0 (54.7–63.6) events per 1,000 person-years.

Figure 9.1 Crude event rate per 1,000 person-years by first exposure to each selected glucose-lowering regimen and average estimated insulin dose over the study period[a]



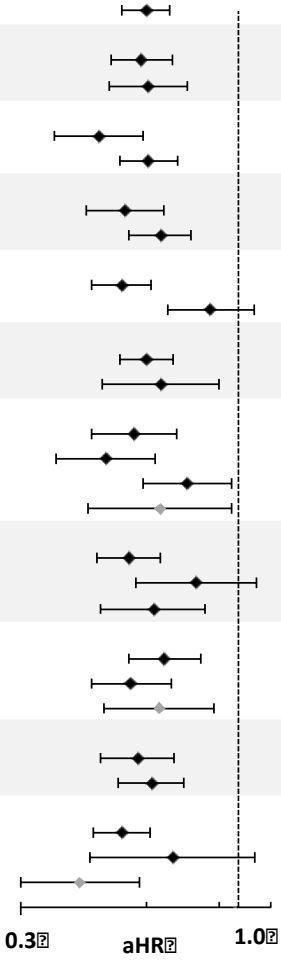
[a] Lower-dose insulin: ≤0.648 units/kg/day; higher-dose insulin: >0.6480 units/kg/day (where the median insulin dose =0.648 units/kg/day). When comparing metformin plus sulfonylurea with the two insulin regimens in the Cox proportional hazards model, duplicate cases were removed. These duplicates have been excluded from the baseline characteristics for the metformin plus sulfonylurea group but not from the two insulin regimens. This is because these duplicate cases are included in the analyses comparing the two insulin regimens only. The number of deaths and combined events in each group were: 186 and 251 for low dose insulin plus metformin, 190 and 309 for high dose insulin and metformin, 492 and 346 for low dose insulin monotherapy and 618 and 522 for high dose insulin monotherapy, respectively. There were 1,027 deaths in people treated with metformin plus sulfonylurea

9.3.3. All-cause mortality

Across all insulin users, the aHR for all-cause mortality in relation to an increase in estimated cumulative average insulin dose of 1 unit/kg/day was 1.48 (95% CI 1.30–1.70). The aHR for patients prescribed concomitant metformin—where patients with no exposure to metformin was used as the reference group—was 0.60 (0.52–0.68) (Figure 9.2). The point estimate for the aHR for patients prescribed concomitant metformin was lower than unity in all subgroups. Tests for heterogeneity revealed a significant interaction between treatment arm and age (p=0.024), HbA1c (p=0.04) and Charlson index (p=0.001), when added as continuous covariates. In addition, the risk of all-cause mortality associated with insulin plus metformin when compared with insulin monotherapy was significantly different in people with or without a history of large vessel disease (aHR = 0.52, 95% CI 0.45–0.62 and 0.86, 95% CI 0.68–1.09, respectively, test for heterogeneity p<0.001). A sensitivity analysis in which insulin exposure was estimated using a variety of methods prior to inclusion into the Cox model gave consistent results (Table 9.3).

For propensity matched patients, the aHR for all-cause mortality for cumulative insulin dose was 1.78 (95% CI 1.41–2.24). The aHR for patients prescribed concomitant metformin was 0.62 (0.52–0.75).

Figure 9.2 Adjusted hazard ratios for all-cause mortality for insulin plus metformin compared with insulin monotherapy



Subgroup	aHR	95%CI	p-value	n/N	p-value for test of heterogeneity
Overall	0.60	(0.52-0.68)	<0.001	1,486/12,020	
Gender			<0.001		
Male	0.58	(0.49-0.69)	<0.001	884/6,829	
Female	0.61	(0.49-0.75)	<0.001	602/5,178	0.89
Age (years)					
≤65	0.46	(0.36-0.59)	<0.001	389/6,699	
>66	0.61	(0.52-0.71)	<0.001	1097/5,315	0.02
Charlson comorbidity index					
≤2	0.53	(0.43-0.66)	<0.001	523/7,071	
≥3	0.65	(0.55-0.77)	<0.001	963/4,924	0.00
Prior large vessel disease					
No	0.52	(0.45-0.62)	<0.001	969/9,472	
Yes	0.86	(0.68-1.09)	0.215	517/2,541	<0.001
Prior cancer					
No	0.60	(0.52-0.70)	<0.001	1,222/10,801	
Yes	0.65	(0.47-0.90)	0.009	264/1,218	0.15
Baseline HbA1c (%)					
≤8.5	0.56	(0.44-0.71)	<0.001	566/4,044	
>8.5 and ≤10.5	0.48	(0.36-0.63)	<0.001	325/3,064	
>10.5	0.76	(0.59-0.97)	0.026	408/3,409	
missing	0.65	(0.44-0.97)	0.033	187/1,479	0.04
Insulin regimen					
Basal-bolus or premix	0.54	(0.46-0.65)	<0.001	952/7,560	
Basal	0.79	(0.57-1.11)	0.174	222/1,884	
Other	0.62	(0.47-0.83)	0.001	312/2,570	0.13
BMI (kg/m2)					
≤28	0.67	(0.55-0.81)	<0.001	696/5,051	
>28	0.55	(0.44-0.69)	<0.001	477/5,067	
Missing	0.65	(0.48-0.87)	0.005	313/1,892	0.36
Diabetes duration (years)					
≤5 years	0.57	(0.47-0.70)	<0.001	623/6,336	
>5 years	0.62	(0.51-0.74)	<0.001	863/5,682	0.32
Creatinine, µmol/l					
<130	0.52	(0.45-0.61)	<0.001	859/8,627	
≥130	0.69	(0.44-1.10)	0.117	377/1,473	
Missing	0.42	(0.30-0.58)	<0.001	250/1,917	0.87

Notes: Insulin dose (units/kg/day) was added as a cumulative dose as an annually updated time-dependent covariate. Prior antihypertensive therapy and history of cancer violated the proportional hazards assumption of the Cox model and so were added as Heaviside functions (<1,095 and ≥1,095 days). When the analysis was split on a covariate, the covariate was removed from the model.

Table 9.3 Sensitivity analysis exploring the effect of different estimations of insulin exposure for the all-cause mortality endpoint in people prescribed insulin monotherapy or insulin in combination with metformin

Analytical approach to insulin dose	aHR for insulin ±metformin					
	All-cause mortality			Combined endpoint		
Insulin dose covariate and model description	aHR	95% CI	p-value	aHR	95% CI	p-value
Baseline continuous insulin dose[a]	0.60	(0.52—0.69)	<0.001	0.71	(0.63—0.81)	<0.001
Continuous time-dependent covariate (cases with missing values excluded)[b]	0.62	(0.53—0.73)	<0.001	0.75	(0.65—0.87)	<0.001
Continuous time-dependent covariate[b]	0.60	(0.52—0.68)	<0.001	0.71	(0.63—0.8)	<0.001
Time-dependent insulin dose group (units/kg/day)[c]	0.59	(0.52—0.68)	<0.001			
Time-dependent insulin dose quartile (units/kg/day)[cd]	0.59	(0.52—0.68)	<0.001			
Time-dependent lag continuous insulin dose (year-1)[e]	0.59	(0.51—0.67)	<0.001	0.71	(0.63—0.8)	<0.001
Time-dependent cumulative continuous insulin dose[f]	0.60	(0.52—0.68)	<0.001	0.71	(0.63—0.8)	<0.001
Time-dependent continuous insulin dose (last year adjusted)[g]	0.59	(0.52—0.68)	<0.001	0.71	(0.62—0.8)	<0.001
Time-dependent quartile of insulin dose (last year adjusted) [dg]	0.63	(0.55—0.72)	<0.001			

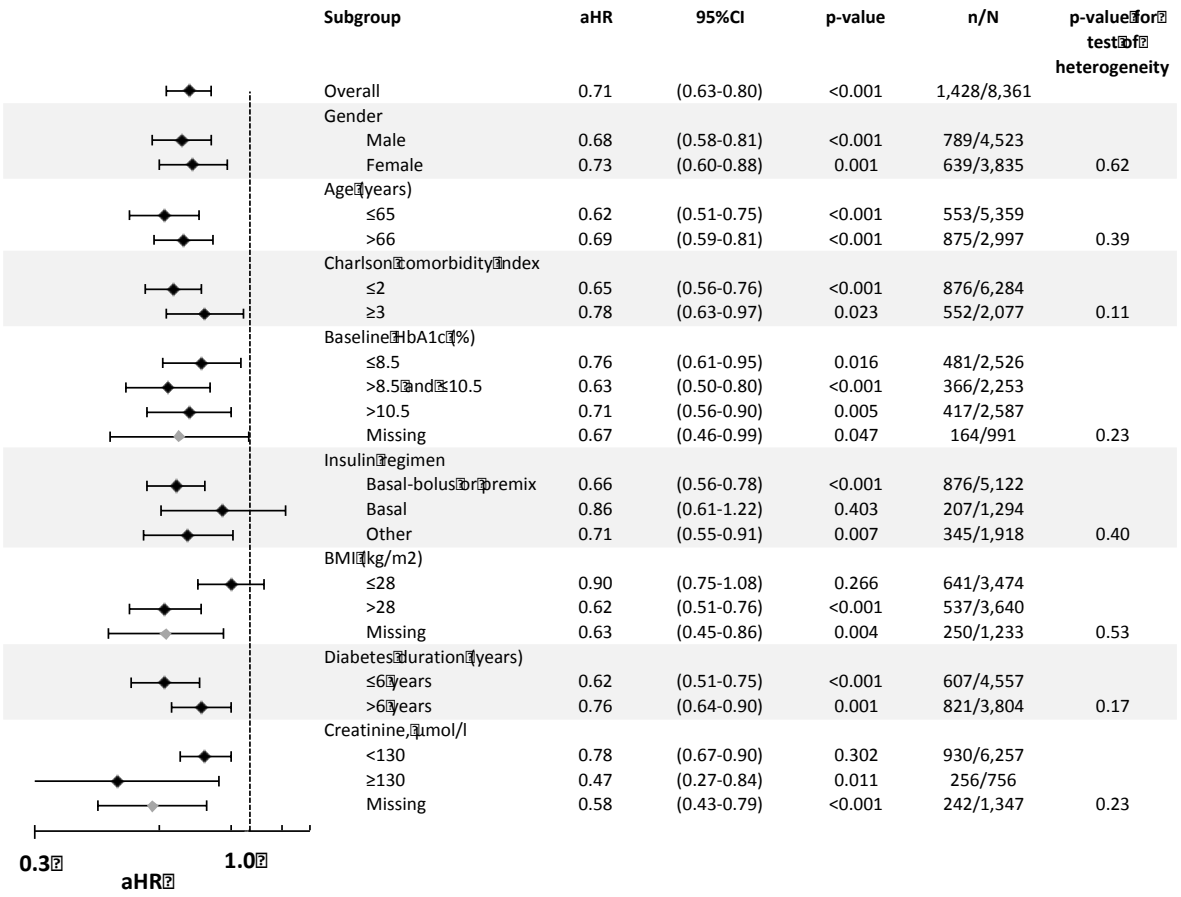
[a] Average daily, weight-standardized insulin dose in year 1, introduced into the Cox model as a continuous covariate.
[b] Yearly-updated average, daily, weight-standardized insulin dose introduced into the Cox model as a continuous covariate.
[c] Yearly-updated average, daily, weight-standardized insulin dose introduced into the Cox model as a categorical covariate.
[d] Provided as there was evidence of a non-linear relationship between insulin dose and endpoint (tested by adding the squared dose as an annually updated covariate into the model in addition to the original annually updated insulin dose covariate and assessing if significant).
[e] As b but a lag of one year applied.
[f] Cumulative weight-standardized insulin exposure was estimated for each subsequent year following insulin initiation and analysed as a time-dependent variable.
[g] The dose for the final part year of the follow-up was take as the average, weight-standardised insulin dose for the 365 day period prior to the censor date for those patients with a follow-up of ≥365 days

9.3.4. Combined endpoint

There was an association between estimated insulin dose and the combined endpoint (aHR=1.35, 95% CI 1.18–1.54, Figure 9.3). Patients treated with concomitant metformin had a reduced risk of the combined endpoint (0.71, 0.63–0.80) when compared to those treated with insulin monotherapy. The point estimate for the aHR for the risk of the combined endpoint in people treated with insulin plus metformin when compared with insulin monotherapy was less than unity for all subgroups and there was no statistically significant difference between subgroups (p-value for test of heterogeneity >0.05 for all subgroups, Figure 9.3).

For propensity matched patients, the aHR for the combined endpoint was 1.68 (95% CI 1.36–2.08). The aHR for patients prescribed concomitant metformin was 0.76 (0.64–0.91).

Figure 9.3 Adjusted hazard ratios for the combined endpoint for insulin plus metformin compared with insulin monotherapy



Notes: Final model specification: insulin exposure, therapy (±metformin), HbA_{1c}, BMI, diabetes duration, index year, insulin regimen, smoking status, serum creatinine, prior cancer, prior large vessel disease, prior lipid-lowering therapy, prior antihypertensive therapy, prior antiplatelet therapy, prior GP contacts, Charlson comorbidity index, gender, and age at index. Insulin dose (units/kg/day) was added as a cumulative dose as an annually updated time-dependent covariate. The number of GP contacts in the year prior violated the proportional hazards assumption of the Cox model and therefore a time interaction for this covariate was also included in the model.

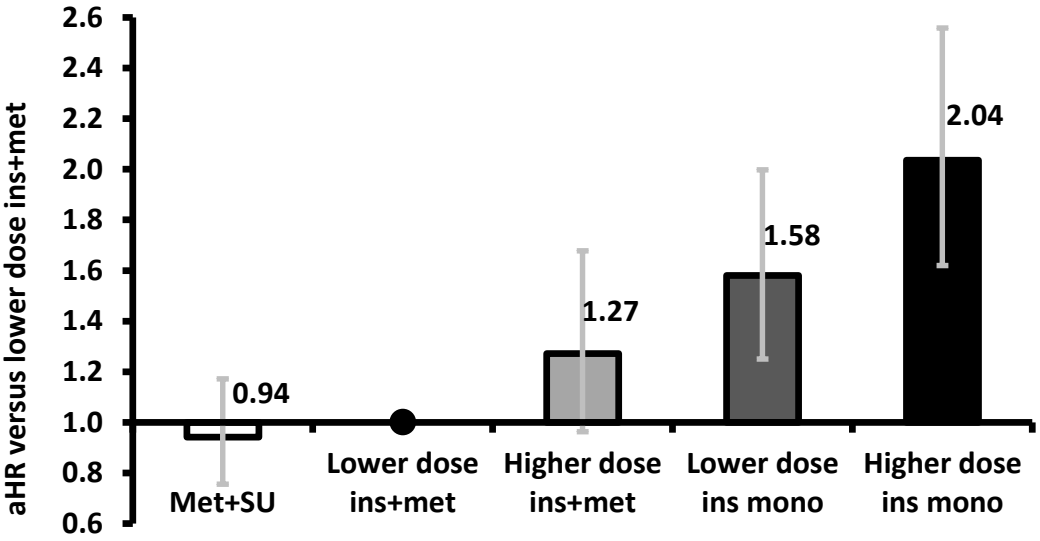
9.3.5. Comparison of lower and higher estimated insulin dose prescribed as monotherapy or in combination with metformin versus sulfonylurea plus metformin

There was an increased risk of all-cause mortality in patients in the higher-dose insulin plus metformin and the lower- and higher-dose insulin monotherapy groups relative to lower-dose insulin plus metformin (aHR 1.27, 0.96–1.68; 1.58, 1.25–2.00; 2.04, 1.62–2.56; respectively Figure 9.4). The aHR for all-cause mortality was similar in people treated with metformin plus sulfonylurea combination therapy and lower-dose insulin plus metformin combination therapy (aHR 0.94, 0.76–1.17). Although not statistically significant, users of higher-dose insulin generally had a higher aHR versus users of lower-dose insulin.

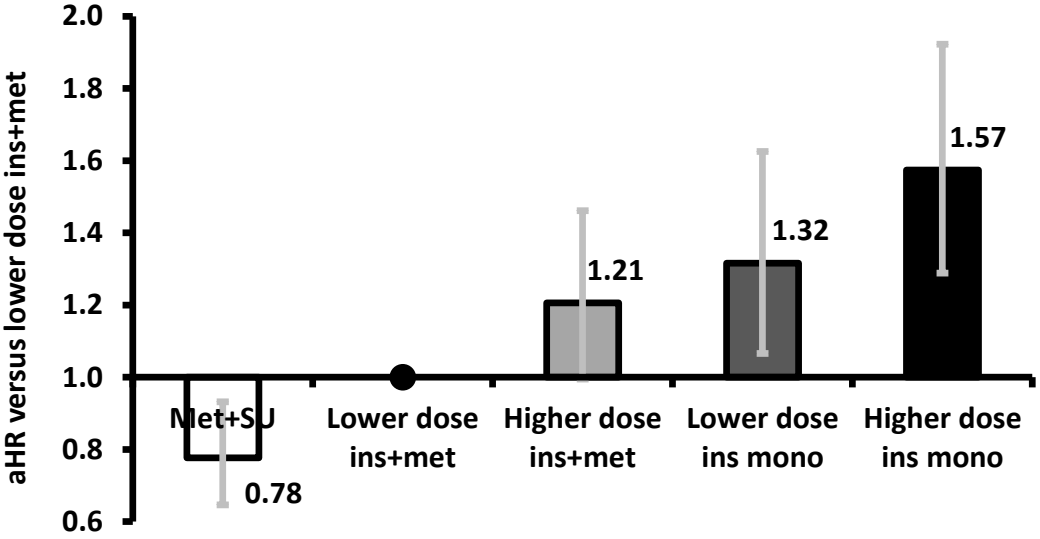
For the combined endpoint, the aHR was significantly lower for people treated with metformin plus sulfonylurea (0.78, 0.65–0.93) and significantly higher for people in the lower and higher dose insulin monotherapy groups (1.32, 1.07–1.63 and 1.57, 1.29–1.92, respectively) when compared with those in the lower dose insulin plus metformin group.

Figure 9.4 Adjusted hazard ratios for a) all-cause mortality and b) the combined endpoint

a)



b)



Notes: Model specification: categorical variable comprising insulin exposure and therapy (metformin plus sulfonylurea, lower and higher dose insulin monotherapy, and lower and higher dose insulin plus metformin), HbA_{1c}, BMI, diabetes duration, index year, smoking status, serum creatinine, prior cancer, prior large vessel disease, prior lipid-lowering therapy, prior antihypertensive therapy, prior antiplatelet therapy, prior GP contacts, Charlson comorbidity index, gender, and age at index. The combined insulin exposure and therapy variable was added to the Cox model as an annually updated time-dependent covariate. Prior cancer violated the proportional hazards assumption of the Cox model and so was entered as a Heaviside function (≤365 and >365 days). Selection criteria: start of therapy occurs between 1 January 2000 and 31 December 2010, aged ≥35 years at diabetes diagnosis, wash-in of ≥180 days prior to diabetes diagnosis, wash-in of ≥365 days between the start of therapy and later of the practice up-to-standard date and the current registration date.

9.4. Discussion

The risk of all-cause mortality and other serious adverse events was reduced markedly in insulin-treated people receiving concomitant metformin. Importantly, we accounted for insulin dose. This finding was stable following propensity score matching.

In the UKPDS, people using metformin had a reduced risk of all-cause mortality, diabetes-related mortality and myocardial infarction versus those treated with standard care even though patients treated with metformin had similar median HbA1c was similar in each treatment arm (7·4% for metformin and 8·0% for the conventional group).[82] This suggests that metformin may have cardioprotective, an effect that cannot be solely explained by its ability to lower blood glucose.[526,527] In addition, *in vitro* studies suggest that metformin may protect against cancer through the activation of activated protein kinase (AMPK).[62] A systematic review carried out by Goudswaard and colleagues demonstrated that insulin plus metformin was associated with less weight gain and reduced insulin requirements compared with insulin monotherapy.[83] However, the studies included in this systematic review were in general of short duration. A more recent systematic review of RCTs conducted by Hemmingsen et al did not find that insulin plus concomitant metformin was associated with a reduced risk of all-cause or cardiovascular mortality compared with insulin alone in people with type 2 diabetes.[528] However, the meta-analysis was again limited by the small number of reported events of interest.[528] The REACH study selected patients with atherothrombosis and showed that treatment with metformin was associated with an aHR for mortality of 0.76 (95% CI 0.65–0.89) compared with no metformin use.[321] The HOME (Hyperinsulinemia: the Outcome of its Metabolic Effects) trial found that the addition of metformin to insulin therapy reduced the risk of macrovascular disease

(0.61, 0.40–0.94).[345] Epidemiological data using CPRD has demonstrated that insulin monotherapy was associated with a significantly higher risk of MACE, cancer, or death than was insulin in combination with metformin (1.51, 1.28–1.78),[61] but this study did not account for insulin dose. Evidence from the Danish National Patient Register found that the aHR for all-cause mortality in comparison with sulfonylurea therapy was 0.96 (0.82–1.13) for insulin plus metformin and 1.14 (1.06–1.20) for insulin monotherapy.[529] In a retrospective observational data using the GPRD, the predecessor of CPRD, van Staa and colleagues determined that differences in cancer risk observed for different glucose-lowering therapies in the 6 months after initiation decreased over time, indicating protopathic bias.[281] However, in this study, people who were censored or experienced an event within 6 months of starting the therapy of interest were excluded from the analysis.

The ORIGIN trial[80] showed that, compared with standard care, low-dose insulin glargine had no statistically significant effect on cancer and cardiovascular outcomes. However, by the end of the study, 47% of the patients allocated to the insulin glargine group were also receiving metformin therapy (compared with 60% in the standard-care group) and 47% of patients in the standard-care group had received treatment with sulfonylureas, and 11% insulin. Here we have shown that, after adjusting for estimated cumulative insulin exposure, people prescribed metformin in combination with insulin had a reduced risk of all-cause mortality in comparison with people prescribed insulin monotherapy, and that people receiving low-dose insulin plus metformin combination therapy had the same outcome as people receiving metformin plus sulfonylurea combination therapy. However, users of metformin plus sulfonylurea had a significantly lower risk of the combined endpoint versus users of lower dose

insulin plus metformin. In a retrospective cohort study, Roumie et al also found that the addition of insulin to existing metformin therapy was associated with an increased risk of non-fatal cardiovascular events and all-cause mortality when compared with the addition of sulfonylureas (aHR 1.30, 95% CI 1.07–1.58).[346] Conversely, Tzoulaki and colleagues found that both FGS and SGS were associated with an increased risk of all-cause mortality relative to insulin monotherapy.[312] The UGDP study found treatment with sulfonylureas to be associated with significantly higher cardiovascular mortality than was treatment with dietary measures alone.[244] One possible explanation for this finding is the impairment of a cardioprotective mechanism known as ischemic preconditioning.[236] However, whilst metformin and sulfonylurea therapy is relatively cheap, insulin is more expensive.[42] Similar results for lower-dose insulin plus metformin and metformin plus sulfonylurea cannot be taken as evidence of insulin's safety. However, the addition of metformin in combination with sulfonylurea has been shown to reduce the risk of MACE, all-cause mortality, and stroke compared with sulfonylurea alone[530] and in this study has been shown to attenuate the risk of all-cause mortality and other serious events when added to insulin. Conversely, data from the UKPDS found that when people with raised FPG (6.1–15.0mmol/l) treated with sulfonylureas were randomised to receive metformin in addition to sulfonylurea or sulfonylurea as monotherapy, the people treated with metformin plus sulfonylurea had a higher risk of all-cause mortality (RR 1.60, 1.02–2.52).[82]

Associations between insulin dose and cancer, and between insulin dose and all-cause mortality have also been reported previously.[255,277,531] Possible explanations for this dose response have been discussed.[525]

9.4.1. Study limitations

There are several potential limitations to consider.[525] Retrospective observational studies can only demonstrate possible associations with events; prospective randomized controlled trials are required to establish causality. Since these data are from routine practice, some data were missing. Two systematic reviews have been conducted to summarise findings from published studies validating diagnoses recorded in CPRD. Khan and colleagues reported that the positive predictive value for most conditions investigated was more than 50%.[367] However, rates of diabetes and musculoskeletal conditions were underestimated.[367] Herrett and colleagues, reported that the median proportion of cases with a confirmed diagnosis was 89% (range 24–100%).[368] Only those patient records meeting CPRD's research quality criteria were included. Rules were applied to maintain consistency in the selection of patients with type 2 diabetes. However, misclassification of diabetes type was possible and was more likely to affect patients prescribed insulin monotherapy.

There were potential limitations to the methods used to estimate insulin dose. Under- and over-estimations of prescribed quantities were possible due to inconsistencies between fields in the prescriptions table or ambiguities in the quantities prescribed, but rules were devised to maintain consistency (Appendix 2). It is also possible that patients using both metformin and insulin may be less compliant with their insulin as this would not be their sole means of controlling blood glucose. The exclusion of people with no weight measurement may have led to the elimination of sicker or more obese patients where weight measurement is more challenging.

One of the main criticisms of this type of observational study is the possibility of confounding by indication. This has been minimized by our selection of only those

patients initiated on insulin for the majority of the analyses; however, differences in the baseline characteristics do exist. To partly address this, patients were matched by propensity score. In addition, subgroup analyses were carried out. There was evidence of a difference in treatment effect for all-cause mortality in the subgroup analyses using age, Charlson index, prior large vessel disease and HbA1c. However, the point estimates for the aHR for all-cause mortality for insulin plus metformin versus insulin monotherapy were less than unity in all subgroups. For the combined endpoint, treatment effect was not significantly different between any of the subgroups tested. Confounding should also be considered when comparing metformin plus sulfonylurea with those on insulin. There is an argument that increasing insulin dose could be a measure of diabetes deterioration. However, when, as a sensitivity analysis, estimated insulin dose was entered into the Cox model as dose in year 1 rather than as a time-dependent covariate, the aHRs were 1.40 (1.22–1.60) for all-cause mortality and 1.22 (1.07–1.40) for the combined endpoint. Due to the risk of lactic acidosis, metformin should be used with caution in renal impairment.[47] From the baseline characteristics, 19% of patients in the insulin monotherapy group had a creatinine level of >130µmol/l in comparison with 3% in the insulin plus metformin group; this did not impact our findings in sensitivity analysis.

The number of events should be at least 10 times the predictor degrees of freedom in the model.[532] Therefore, over-fitting of the model may have occurred for some of the subgroup analyses.

9.4.2. Conclusion

People with type 2 diabetes treated with insulin plus concomitant metformin had a markedly reduced risk of death and other serious outcomes compared with people treated with insulin monotherapy. Studies are needed to determine the risks and benefits of injecting insulin in type 2 diabetes, and the possible benefits associated with the administration of concomitant metformin.

10. Discussion of overall findings

10.1. Main findings

10.1.1. Summary

Between 1991 and 2010, the estimated incidence and prevalence of clinically diagnosed and recorded type 2 diabetes increased three-fold and the estimated number of people with diagnosed and recorded type 2 diabetes treated with insulin increased seven-fold. Estimated insulin dose was associated with an increased risk of all-cause mortality and other serious adverse events in people with type 2 diabetes receiving insulin with or without metformin, however, the use of metformin in combination with insulin was associated with a reduction in risk compared with insulin alone.

10.1.2. Specific findings

There has been a significant increase in the clinically diagnosed and recorded incidence of type 2 diabetes between 1991 and 2010 from 169 to 515 cases per 100,000 person-years (Chapter 4). The percentage of patients with a recorded diagnosis for type 2 diabetes before the age of 40 also increased with each increasing 5-year calendar period (5.9% in 1991–1995, 8.4% in 1996–2000, 8.5% in 2001–2005 and 12.4% in 2006–2010, respectively). In addition, the estimated crude prevalence of type 2 diabetes trebled between 1991 and 2012 (increasing from 1.32% to 4.54%, Chapter 5).

The estimated number of people with type 2 diabetes treated with insulin increased seven-fold between 1991 and 2010 from 37.0 (95%CI 30.2–46.2) thousand to 277.4 (262.8–293.3) thousand (Chapter 6). During the same period, the proportion of people

with type 2 diabetes treated with insulin was estimated to have increased from 5% to 15%. In addition, over a 10-year period, the total annual cost of insulin increased from £156 million in 2000 to £359 million in 2009, an increase of 130% (Chapter 7). Although an increase in prescribing of the more expensive insulin analogues has contributed to this increase in spending on insulin, the volume of insulin prescribed also increased during the same period. The percentage of people with type 2 diabetes treated with insulin prescribed as monotherapy decreased from 97% to 37% between 1991 and 2010, while the percentage of people prescribed insulin in combination with metformin increased to 43%.

Improved glycaemic control and survival was observed in people with type 2 diabetes. Mean HbA_{1c} for type 2 diabetes decreased from 8.4% in 1991 to 7.5% in 2003 but then plateaued. For type 2 diabetes HbA_{1c} levels were highest in people receiving insulin therapy and remained relatively constant from 1992 onwards (HbA_{1c} levels between 8.4% and 8.7%). For type 2 diabetes, survival increased between 1991 and 2013 where the aHR for all-cause mortality was 1.75 (1.60–1.92) in 1991 and 0.58 (0.48–0.70) in 2013 (where 2001 was taken as the reference year). The average life expectancy for incident treated type 2 diabetes increased by around eight years between 1991 and 2009.

Estimated insulin dose was associated with an increased risk of all-cause mortality in people with type 2 diabetes receiving insulin monotherapy (aHR 1.54, 95% CI 1.32–1.78, for 1 unit/kg/day increase in insulin dose, Chapter 8) and in those treated with insulin with or without metformin (1.48, 1.31–1.70, Chapter 9). However, the use of metformin in combination with insulin was associated with a reduction in risk of all-

cause mortality when compared with insulin alone (0.60, 0.52–0.68). This reduction in risk was also observed following propensity score matching (0.62, 0.52–0.75).

10.2. Study strengths and limitations

The advantages and disadvantages of retrospective observational studies have been described in Chapter 3. In addition, the strengths and limitations of the studies conducted have been described in detail at the end of each chapter. This series of retrospective, observational studies have several advantages. Despite the cost of data acquisition, retrospective observational studies are considerably cheaper to carry out when compared with RCTs. Due to the size of CPRD GOLD (approximately 12 million patients), the sample size for each study was relatively large and the follow-up time was moderate. The data in CPRD have already been collected and collated, therefore, these retrospective observational studies could be completed more quickly than an RCT. CPRD GOLD is thought to be representative of the general population in the UK in terms of age and gender structure and crude mortality.[364,365] In a systematic review, Khan and colleagues reported that the positive predictive value for most conditions investigated was more than 50% and 14 of the conditions investigating had a positive predictive value of more than 90%.[367] In a more recently conducted systematic review, Herrett and colleagues reported that the median proportion of cases with a diagnosis confirmed by data within CPRD or from an external resource was 89% (range 24–100%).[368] Similar results have been reported when a study originally carried out using data from CPRD was replicated using data from QResearch.[533] A cohort study with nested case-control analysis investigating the association between statin use and the risk of mortality in patients with ischaemic heart disease carried out using data from

CPRD reported that patients taking statins had a 55% decreased risk of death in the cohort analysis and a 31% lower odds of death in the case-control analysis.[533] The corresponding results using data from QResearch were 53% and 39%, respectively.[533]

Statistical methods were used to adjust for potential confounding factors. In retrospective observational studies, only those people who have actually been prescribed the therapy or therapies of interest in the real world are included in the study and are therefore more likely to reflect clinical practice when compared with RCTs which can apply strict inclusion and exclusion criteria. In addition, RCTs are subject to selection bias as they include only those people who have consented to be part of the study. In addition, observational studies can be used to answer questions that would be difficult to answer using any other study design.

This series of retrospective observational studies also have some limitations. The data recorded in CPRD GOLD has been recorded by the primary care physician as part of the routine care of the patients and not for the purposes of research. Primary care physicians are therefore likely to record only the information that they consider to be important in terms of the ongoing care of the patient. Missing values were unlikely to be missing completely at random. For example, patients with poor glycaemic control may have more frequent HbA1c tests and GPs may be more likely to record a BMI if the patient is obese. In a validation study exploring the effect of antihypertensive therapy on blood pressure in GPRD, Delaney and colleagues found that missing blood pressure data was not missing completely at random.[534] Multiple imputation was used to impute missing values for the studies described in Chapters 8 and 9.

Changes in coding during the study period including overall improvements in recording and changes in terminology from IDDM and NIDDM to type 1 and type 2 diabetes may

have impacted on case selection. Misclassification of patients with a diagnosis of IDDM as type 1 instead of type 2 would have led to an underestimation in the incidence and prevalence of diagnosed type 2 diabetes and is more likely to have affected years prior to 1997, when this terminology was used more often.[367] Consequently, the increase in the estimated incidence and prevalence of diagnosed and recorded type 2 diabetes may be exaggerated. The distinction between type 1 and type 2 diabetes is problematic due to the presence of conflicting diagnoses and prescriptions in some patient histories. However, robust selection criteria were used throughout. Increased prescribing of insulin in type 2 diabetes (Chapter 6) may have led to greater misclassification of type 2 diabetes as type 1 diabetes over time, which could have impacted on prevalence and survival estimates. Information recorded as free text in CPRD was not accessed, as data stored as free text are not routinely provided as part of CPRD, incur a financial cost and are challenging to analyse. Therefore, patients with diagnoses recorded as free text as opposed to Read code were not identifiable. The use of free text fields is likely to depend on the user and the GP system used. Free text recorded within the Vision system is always linked to specific coded data.[359]

Validation of type 2 diabetes recording in CPRD was not carried out. However, De Lusignan and colleagues investigated miscoding, misclassification and misdiagnosis of diabetes in primary care and found that 5.8% of patients with diabetes had potential classification errors. However, of the 5.8% of people identified with potential classification errors, only 40% were confirmed to have had errors in their diabetes coding.[535] Patient consultation rates for diabetes have been reported to be lower in GPRD when compared with those obtained from the MSGP4 in a study conducted between September 1991 and August 1992.[464] However, data recording requirements differed between sources.[464] A chronic condition need only be recorded at the time of

diagnosis in GPRD whereas every consultation was recorded in the MSGP4.[464] For the prevalence study described in Chapter 5, patients remained a prevalent case from the date of presentation until the end of their recorded data. A systematic review of measures of data quality in primary care electronic patients records found that a consistently high positive predictive value was reported by included studies but prescribing data were found to be more sensitive when compared to diagnostic and lifestyle data.[536] This suggests that the use of both diagnoses for diabetes and prescriptions for glucose-lowering therapies in the selection of patients will have led to improved case selection. When identifying incident cases of type 2 diabetes, a wash-in was applied in order to exclude patients with prevalent disease. However, the incidence of newly diagnosed type 2 diabetes may be higher in the first few months following registration at a GP practice as routine health checks associated with the registration process[537] may include a test for diabetes. Therefore, excluding patients without the specified wash-in period may have led us to underestimate the incidence of type 2 diabetes.

Several of the studies conducted utilised CPRD-linked HES data in order to improve the capture of health events occurring in secondary care. The use of other linked datasets including ONS mortality data and MINAP (at an additional cost) could have been considered. Linked datasets are only available for a proportion of the CPRD population registered at English practices. ONS mortality data provides the date of death and the cause of death (post 1st January 2001) for English practices consenting to participate in the linkage scheme. However, it has been reported by GPRD that 99.2% of acceptable patients registered at linked practices who die on or after 1st January 2001 and have a recorded cause of death were also identified as dead in GPRD, where the mean and median death date differences were 3.65 and 0 days, respectively (unpublished data).

In a study conducted by Herrett and colleagues, the crude incidence of myocardial infarction was reported to be 25% lower when only CPRD was used when compared to the use of CPRD, HES and ONS mortality data combined.[538] However, when compared with MINAP, the positive predictive value of acute myocardial infarction recorded in CPRD and HES was 92.2% (95% CI 9.16%–92.8%) and 91.5% (90.8%–92.1%), respectively.[538]

There were limitations associated with using diagnosed and recorded incidence and prevalence of type 2 diabetes in order to understand the true incidence and prevalence of the condition. The incidence and prevalence of type 2 diabetes has been estimated from 1991–2010 and 1991–2013, respectively. The recording of diabetes may have improved during this time. The introduction of QOF in 2004 incentivised GPs to keep adequate records of patients with diabetes.[404] In 1993, 90% of practices were computerised, however, only 8% were paperless.[539] In a review published by employees of GPRD, it was suggested that post-2000, the dataset was more clinically rich due to the use of the more complex but easier to use Vision system.[359] However, in a study of people using non-steroidal anti-inflammatory drugs conducted between November 1989 and February 1991 by Jick and colleagues, it was found that 87% of diagnoses recorded in consultation letters were also present in the computer record.[369] Only acceptable patients registered at up-to-standard practices were used for this series of studies.

A prescription recorded in the therapy table in CPRD indicates an intention to treat on the part of the primary care physician. The proportion of prescribed medications actually dispensed to and taken by the patient is unknown. Insulin dose was not routinely recorded in CPRD and was therefore estimated from the quantity of insulin

prescribed. Limitations associated with the estimation of insulin dose have been discussed in detail in Chapter 8. The distribution of insulin dose was heavily skewed with a long right hand tail. Patients who switch between insulin types are likely to waste more insulin leading to an overestimate in daily dose. These patients may have worse glycaemic control and outcomes when compared with those patients who remain stable on the same insulin product.

Epidemiological studies are often criticized because of the risk of a form of analytical bias that is termed confounding by indication. That is, those treated with insulin are at a more advanced stage in the natural history of the disease or they have phenotypic characteristics that require a switch to insulin. The risk of this bias was minimised as only those patients prescribed insulin were selected. However, increasing insulin dose is likely to be a measure of diabetes deterioration. This confounding bias is likely to favour the lower doses of insulin. In order to minimise this bias, statistical methods that adjusted for various confounders, including duration of diagnosed diabetes, age, comorbidities and baseline HbA1c, were used. In addition, several sensitivity analyses were conducted in order to explore the effect of different estimations of insulin dose on the study endpoints. These different estimations in order to overcome possible limitations including change in insulin dose prior to endpoint and fluctuations in insulin dose due to intermittent collection of prescriptions.

Unlike an RCT, patients were not randomised to receive insulin monotherapy or insulin plus metformin. The reason why patients prescribed insulin monotherapy did not receive concomitant therapy with metformin was not clear. Current guidelines recommend that metformin should be continued when insulin is initiated.[7,55] However, in 2010, 43% of people with insulin treated type 2 diabetes did not appear to be

receiving metformin concomitantly. Some of these people could have had other concomitant conditions that lead to an increased risk of lactic acidosis, for example renal impairment, dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment, or recent myocardial infarction.[47] Metformin is also associated with a greater than 1 in 10 risk of gastrointestinal side effects on initiation.[540] Gastrointestinal side effects can resolve spontaneously following initiation, but may persist in some people, particularly when high doses are prescribed.[47] A trial of a modified release formulation is recommended by NICE in people with gastrointestinal side effects that could lead to discontinuation of metformin.[54] However, it is possible that gastrointestinal side effects could lead to poor compliance or discontinuation in some patients. Median serum creatinine levels were higher in the insulin monotherapy group when compared with those treated with insulin plus metformin (Table 9.1). If patients with contraindications to metformin are more likely to receive insulin as monotherapy, this is likely to have resulted in a bias that favoured insulin plus metformin. In order to minimise the risk of this bias, statistical methods were used that adjusted for known confounders including serum creatinine. In addition, propensity score matching was carried out.

The endpoints used for the studies in Chapters 8 and 9 are also potential complications of diabetes as discussed in Chapter 2. Statistical methods were adopted that adjusted for many baseline covariates, however, there exists the possibility that outcome depended on factors that were either known or unknown that could not be fully adjusted for in the Cox proportional hazards model. Retrospective observational studies can only demonstrate possible associations with events; prospective randomised controlled trials are required to establish causality. Comparison between results obtained from RCTs and observational studies vary with some reporting

comparable results[349,350] and others reporting differences in the estimated magnitude of treatment effects but good correlation between the different study types.[240] Registration of the study protocol prior to carrying out the study would increase transparency and reduce the risk of publication and reporting bias.

10.3. Study implications and future research

The estimated prevalence and incidence of diagnosed and recorded type 2 diabetes has increased. The proportion of earlier onset type 2 diabetes continued to increase as a proportion of those diagnosed and these people have a greater opportunity to develop long-term complications. The study results could be explained, at least in part, by a true increase in type 2 diabetes in the UK population due to changes in diet and lifestyle leading to a rise in obesity.[63] In addition, an increase in life expectancy in the UK population[541] and survival in type 2 diabetes (Chapter 5) has also contributed to an increase in prevalence of the condition. However, other explanations for this trend also exist. Due to the limitations in the recording of type 2 diabetes in CPRD, our estimates of the prevalence and incidence of type 2 diabetes are likely to be conservative. However, during the study period, improved recording of diagnoses may have played a part in the trends observed. Furthermore, only the incidence and prevalence of diagnosed type 2 diabetes could be estimated. The corresponding rates of undiagnosed type 2 diabetes remain unknown. Changes in diagnostic thresholds increased the number of people who were labelled as having type 2 diabetes. Enhanced detection of diabetes may have reduced the time between the true onset of type 2 diabetes and its diagnosis, which will reduce the population of undiagnosed cases. The introduction of QOF incentivised both the identification, recording and

monitoring of people with type 2 diabetes. This could be viewed positively as patients will receive appropriate diabetes care at an earlier stage of their disease. The relative contributions that each component has made to the increase in incidence and prevalence observed remains unknown. However, measures to reduce obesity through healthy eating and increased exercise need to remain top of the agenda with respect to health policy in the UK in order to have an impact on diabetes prevalence in the future.

In Chapter 4, a decrease in the estimated incidence of diagnosed and recorded type 2 diabetes in the UK between 2009 and 2010 from 533 to 515 newly diagnosed people per 100,000 person-years was reported.[421] Furthermore, several studies have reported that the incidence and prevalence of diabetes in the US has remained relatively stable in recent years.[423,542,543] The increase in the estimated prevalence of diagnosed and recorded type 2 diabetes between 2012 and 2013 was less than expected based on the rate of increase observed prior to 2012. However, further research is required to determine whether the incidence and prevalence of diagnosed type 2 diabetes in the UK is starting to plateau.

Survival in people with type 2 diabetes increased between 1991 and 2013, suggesting that the overall management of this condition has improved. Although glycaemic control improved initially, HbA_{1c} levels remained relatively constant between 2003 and 2013. Therefore, improvements in survival may not be fully explained by improved glycaemic control. In several meta-analyses, intensive glucose control has not been associated with a significantly different risk in all-cause mortality when compared with conventional control of blood glucose.[111,202,219] Improvements in blood pressure and total cholesterol were observed during the study period and more patients were

prescribed antiplatelet, antihypertensive and lipid-lowering therapy. Tighter control of blood pressure has been shown to be associated with a reduction in the risk of deaths and complications related to diabetes.[46] The results from ADVANCE demonstrated that people assigned to indapamide and perindopril had improved reduction in blood pressure versus placebo and lower risk of major vascular events and deaths (RR 0·82, 95%CI 0·68–0·98 cardiovascular death and 0·86, 0·75–0·98 for all-cause mortality).[544] However, for ACCORD, intensive control of systolic blood pressure statistically, significantly reduced the risk of stroke (aHR .59, 95% CI 0.39–0.89 for any stroke and 0.63, 0.41–0.96 for non-fatal stroke) but not the rate of a composite outcome of fatal and non-fatal major cardiovascular events. The use of statins has been shown to reduce the risk of coronary and vascular events.[545] Aspirin has been shown to have a protective effect in people with established cardiovascular disease.[546] In a study conducted by Vamos and colleagues using GPRD, the introduction of QOF was associated with improvements in blood pressure and total cholesterol, which were greater than could be predicted from trends prior to the introduction of QOF.[547] However, no significant additional improvement was observed for glycaemic control.[547] Improvements in survival could also be related to the early detection of type 2 diabetes. A retrospective study using data from GPRD carried out a longitudinal analysis of achievement rates for 42 QOF indicators including four diabetes quality indicators to identify patients with a recorded HbA_{1c} , blood pressure, total cholesterol and serum creatinine measurement.[548] Achievement rates improved in the years prior to the introduction of QOF (2001-2002 and 2002-2003) before reaching a plateau after 2004–2005.[548] A small detrimental effect was observed for non-incentivised aspects of patient care.[548] However, the impact of changes in data recording procedures on these results was not investigated.[548]

The number of people with type 2 diabetes treated with insulin increased considerably between 1991 and 2010. Findings from UKPDS in 1998, recommendations from NICE in 2002 and the introduction of QOF in 2004 could have advocated and incentivised tighter glucose control.[67,404,549] In a recent retrospective study carried out using data from GPRD, it was reported that a greater proportion of people with diabetes were iniated on glucose-lowering therapy within one or two years of diagnosis following the introduction of QOF.[550] Marketing of the new insulin analogues, which are thought to be associated with a lower risk of hypoglycaemia and have a longer duration of action, may have also reduced the barriers to insulin initiation. However, the baseline characteristics of patients starting insulin did not support the theory of earlier insulin initiation. Therefore, the increase in insulin use in type 2 diabetes may reflect a true change in the population of people with type 2 diabetes with an increase in the proportion of people with more advanced disease due to improved survival. The increasing prevalence of insulin also partly reflects an increase in the overall prevalence of type 2 diabetes. The use of insulin in type 2 diabetes is common. Therefore, it is vital to understand the risks and benefits of insulin use in type 2 diabetes, determine when it should be prescribed and characterise the patients who will benefit most from this type of glucose-lowering therapy.

Increasing insulin exposure has been shown to be associated with an increased risk of all-cause mortality, MACE and cancer in Chapters 8 and 9 and elsewhere.[255] Chapter 6 has shown that any risks associated with insulin could affect an estimated 277,000 people in the UK with type 2 diabetes and currently using insulin (2010 figures). As discussed in Chapter 3, epidemiological studies can only show associations between insulin use and risks and it is possible that residual bias or confounding could account for the results. The results of ORIGIN indicated that insulin use had no statistically

significant effect on cardiovascular or cancer risk.[80] While this provides some reassurance, the people selected did not reflect those patients who receive insulin in the real world.[80] Although, insulin use was not associated with a significant increase in the risk of cardiovascular events, no statistically significant decrease in the risk of these events was observed either. Insulin is costly and needs to be injected. In addition, the risk of weight gain and hypoglycaemia is higher with insulin compared with other glucose-lowering therapies.[80,171,191,209,210] Further research is therefore required in order to investigate these results.

Not starting insulin and leaving patients in a state of hyperglycaemia is also not an attractive option for clinicians and is associated with increased risk of developing diabetic complications.[67] Despite this, a recent retrospective cohort study has reported that treatment intensification with oral glucose-lowering therapies or insulin is delayed despite poor glucose control.[461] It is likely that insulin will become necessary for a proportion of people with type 2 diabetes due to the progressive loss of beta-cell function over time. Further research could be conducted to determine the potential predictors of a good response to insulin, taking into account both the change in HbA_{1c} and weight and the risk of hypoglycaemia, all-cause mortality, cardiovascular events and cancer. Unlike some other medical conditions, diabetes outcomes depend not only on pharmacological interventions but also, importantly, on the willingness of the patient to make necessary adjustments to their lifestyle.

The results of Chapter 9 suggest that insulin can be prescribed in a way that reduces the possible risk associated with this therapy. When metformin was prescribed in combination with insulin, there was a substantial decrease in the risk of all-cause mortality by approximately half. Compared with insulin monotherapy, insulin in

combination with metformin has been found to be associated with less weight gain, reduced insulin requirements, and a reduced risk of macrovascular disease, MACE, cancer and all-cause mortality.[61,83,345,529] Conversely, a systematic review of RCTs conducted by Hemmingsen and colleagues did not find that insulin plus concomitant metformin was associated with a reduced risk of all-cause or cardiovascular mortality compared with insulin alone in people with type 2 diabetes but the number of events reported was small.[528] However, a recently published retrospective study found that the addition of insulin to metformin was associated with an increased risk of a composite of nonfatal cardiovascular outcomes and all-cause mortality when compared with the addition of a sulfonylurea (aHR 1.30, 95% CI 1.07–1.58).[346]

Several RCTs have compared the effect of glucose-lowering therapies on glycaemic control but there is a lack of RCT data using hard outcomes such as cardiovascular events, cancer and death. As tight glycaemic control was only shown to significantly reduce the risk of macrovascular complications in the follow-up study to the UKPDS, and not in the original UKPDS, ACCORD, VADT or ADVANCE studies,[67,79,217,218] interventional studies using hard endpoints may be preferred in order to further investigate the risks and benefits of exogenous insulin in type 2 diabetes.

Both NICE and ADA/EASD guidelines recommend that when insulin is initiated, it is added to existing metformin therapy in patients with type 2 diabetes.[7,55] The findings from Chapter 9 are in agreement with this recommendation and therefore help to reinforce existing clinical guidelines. This study occupies level 2 on Oxford Centre for Evidence-based Medicine's Levels of Evidence.[225] However, epidemiological studies are often criticized because of the risk of a form of analytical bias that is termed confounding by indication. The endpoint and the therapy of interest may be associated

with a confounding factor or the increased risk of the endpoint of interest may predispose that patient to receiving a particular therapy. Therefore, interventional trial designs could be used to further investigate the results produced in Chapters 8 and 9. However, consideration would need to be given to the principle of clinical equipoise. In an RCT, clinical equipoise describes a state of genuine uncertainty in the medical community as to whether one treatment arm will be superior to the other. The evidence base for metformin may be such that the state of clinical equipoise does not exist rendering the commencement of a clinical trial unethical. Even in situations where metformin is usually contraindicated and there is more uncertainty as to whether metformin therapy is beneficial, the state of clinical equipoise may still be difficult to achieve. Eurich and colleagues attempted to conduct a pilot study to investigate the effect of metformin on functionality, morbidity, and mortality outcomes in patients with type 2 diabetes and heart failure using a double blinded randomised placebo controlled design.[551] However, the uncertainty that appeared to exist in the scientific community as to the beneficial impact of metformin in a situation where it is normally contraindicated did not apply in clinical practice where more than 50% of patients were already receiving metformin at baseline.[551]

However, contrary to this, in real-world clinical practice, insulin is still prescribed as monotherapy for a large proportion of insulin treated patients (43% in 2010). Although the proportion of people in which metformin could not be prescribed due to contraindications or side effects was not identified, this could illustrate that insulin monotherapy is seen as an alternative to insulin plus metformin. In terms of RCTs using hard clinical endpoints, guidelines supporting the use of metformin in type 2 diabetes are largely based on results from UKPDS which reported that patients randomised to metformin therapy had a reduced risk of all-cause mortality (36%, 95% CI 9%–55%)

and any diabetes related endpoint (32%, 13%–47%) when compared with conventional therapy.[82] The Michael Berger debate at the 2014 EASD annual meeting illustrates that some of the scientific community believe the evidence base for metformin is not strong enough.[552] The Glucose Lowering In Non-diabetic hyperglycaemia Trial (GLINT) is currently being conducted.[553] This illustrates that, dependingon the study design, RCTs investigating the risks and benefits of metformin on hard clinical endpoints remain feasible. The results from this study will provide important evidence on the use of metformin in the prevention of cardiovascular outcomes.[553]

Metformin plus a sulfonylurea are recommended as a second-line glucose lowering regimen for type 2 diabetes by NICE.[55] When insulin is initiated, NICE recommends that it should be added to the metformin plus sulfonylurea combination.[55] However, the number of people identified who were prescribed insulin in combination with metformin plus sulfonylurea and met the selection criteria outlined in Chapter 9 was small. In addition, the benefits of combining insulin with newer agents could be further investigated. A recent review by Frandsen and Madsbad has shown that the addition of a DPP4-inhibitor to insulin therapy is associated a moderate effect on HbA_{1c}, no effect on weight and no increased risk of hypoglycaemia.[554] The risk of all-cause mortality, MACE and cancer associated with insulin in combination with other glucose-lowering therapies is an important area for future research.

New glucose-lowering medications such as GLP-1 agonists, DPP-4 inhibitors and SGLT-2 inhibitors have been approved for the control of blood glucose in type 2 diabetes in the last decade.[69] In fact, NICE guidelines suggest that a DPP-4 inhibitor, GLP-1 agonist or a thiazolidinedione could be used as an alternative to insulin as third-line therapy in type 2 diabetes.[55] A potential area for future research could be to investigate whether

any of these new therapies (alone or in combination with other types of glucose-lowering medications) provide better or worse outcomes in comparison with insulin at the same stage of the treatment pathway.

Due to its theoretically unlimited potential to lower blood glucose, it is likely that insulin will remain the mainstay for people with hyperglycaemia that cannot be controlled using non-insulin glucose-lowering medicines.

10.4. Conclusion

The estimated prevalence of diagnosed and recorded type 2 diabetes is increasing. Furthermore, the proportion of people diagnosed at a relatively early age (<40) is also increasing. Measures to tackle obesity in the UK (e.g. the UK government Change for Life scheme[555]) are important in order to curb this trend.

Insulin has become a commonly prescribed therapy for the control of blood glucose in type 2 diabetes and at a large financial cost to the NHS. Therefore, it is important to understand the full risks and benefits associated with insulin for the management of hyperglycaemia in type 2 diabetes. Current NICE, ADA and EASD guidelines recommend that metformin therapy should be continued when insulin is initiated. [7,55] The results of this thesis are in support of this recommendation.

An association between estimated insulin dose and an increased risk of MACE, cancer and all-cause mortality has been demonstrated. The risk of all-cause mortality and other serious adverse events was reduced markedly in insulin- treated people receiving concomitant metformin. However, retrospective observational studies do have limitations. Despite statistical adjustment for many known confounders, these

studies can still be criticised due to the potential for the results to be attributed to factors that are either unknown or cannot be fully adjusted for. Therefore, changes in clinical practice cannot be recommended based on this study alone.

The results presented in this thesis and the results of previously published observational studies[60–62,223,224,251,253,255,259,260,270–272,279,346] are discordant with the findings from the most relevant RCT conducted, ORIGIN. However, study subjects were treated with insulin earlier in their treatment pathway compared with those who receive insulin in normal clinical practice. The results of this thesis suggest that further research is required in order to improve our understanding of the risks and benefits of exogenous insulin in type 2 diabetes.

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12. Further acknowledgements

Chapters 4 to 9 have been prepared as manuscripts for publication and 4 of the chapters have already been published. The co-authors of these manuscripts and their contribution to the work presented in this thesis are described in Table 12.1.

Table 12.1 Contributions of co-authors

Name	Contributions	Chapters
Prof Craig Currie	Selection of data source Study design Advice on data analysis Interpretation of results Editing	All
Sara Jenkins-Jones	Data extraction from CPRD flat files Editing	4, 5, 6, 8 and 9
Christopher Ll. Morgan	Advice on data analysis Interpretation of results Estimation of the proportion of people with type 1 and type 2 diabetes	4, 5, 7 and 8 7
Dr Chris Poole	Study design Data interpretation Editing	4 and 7
Dr Guntram Schernthaner	Interpretation of results Editing	5 and 8
Dr John Peters	Interpretation of results Editing	1, 2, 3, 4, 5 and 10
Prof Anthony Barnett	Interpretation of results Editing	4
Prof Edwin Gale	Interpretation of the results Editing	6

13. Appendices

13.1. Appendix 1 List of publications and conference proceedings

13.1.1. Publications

1. Holden SE, Jenkins-Jones S, Morgan CL, Schernthaner G, Currie CJ. Glucose-lowering with exogenous insulin monotherapy in type 2 diabetes: dose association with all-cause mortality, cardiovascular events, and incident cancer. Diabetes Obes Metab. 2015 17:350-62.
2. Bannister CA, Holden SE, Jenkins-Jones S, Morgan CL, Halcox JP, Schernthaner G, Mukherjee J, Currie CJ. Can people with type 2 diabetes live longer than those without? A comparison of mortality in people initiated with metformin or sulphonylurea monotherapy and matched, non-diabetic controls. Diabetes Obes Metab 2014.;16:1165-73.
3. Currie CJ, Holden SE. Optimising clinical outcomes resulting from glucose lowering therapies in type 2 diabetes: increased confidence about the DPP-4 inhibitors and continued concerns regarding sulfonylureas and exogenous insulin. Diabetes Obes Metab 2014;16:881-4.
4. Holden SE, Bannister CA, Currie CJ. Mortality after cancer among patients with diabetes mellitus: effect of diabetes duration and treatment: (questionable) classification of diabetic patients based on combination of specific glucose-lowering drugs. *Diabetologia* 2014;57:2001-2.
5. Morgan CL, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Combination therapy with metformin plus sulfonylureas versus metformin plus DPP-4 inhibitors: association with major adverse cardiovascular events and all-cause mortality. *Diabetes Obes Metab* 2014;16:977-83

6. Morgan CL, Mukherjee J, Jenkins-Jones S, Holden SE, Currie CJ. Association between first-line monotherapy with sulfonylurea versus metformin and risk of all-cause mortality and cardiovascular events: a retrospective, observational study. *Diabetes Obes Metab* 2014;16:977-83
7. Holden S, Currie C. Insulin therapy in people with type 2 diabetes: is it safe in terms of the risk of cardiovascular disease, cancer and all-cause mortality? *Diabetes Voice* 2014;59:40–41.
8. Holden SE, Currie CJ. Mortality risk with sulfonylureas compared to metformin. *Diabetes Obes Metab* 2014;16:885-90.
9. Holden SE, Gale EA, Jenkins-Jones S, Currie CJ. How many people inject insulin? UK estimates from 1991 to 2010. *Diabetes Obes Metab* 2014;16:553-9.
10. Holden SE, Barnett AH, Peters JR, Jenkins-Jones S, Poole CD, Morgan CL, Currie CJ. The incidence of type 2 diabetes in the United Kingdom from 1991 to 2010. *Diabetes Obes Metab* 2013;15:844-852.
11. Holden SE. Comment on 'impact of UK Medical Eligibility Criteria implementation on prescribing of combined hormonal contraceptives'. *J Fam Plann Reprod Health Care* 2013;39:229-30.
12. Holden SE, Jenkins-Jones S, Poole CD, Morgan CL, Coghill D, Currie CJ. The prevalence and incidence, resource use and financial costs of treating people with attention deficit/hyperactivity disorder (ADHD) in the United Kingdom (1998 to 2010). *Child Adolesc Psychiatry Ment Health* 2013;7:34.
13. Holden SE. Gluten-free foods and the cost of prescriptions. *J Hum Nutr Diet* 2012;25:405

14. Holden SE, Currie CJ. Endogenous hyperinsulinaemia and exogenous insulin: a common theme between atherosclerosis, increased cancer risk and other morbidities. *Atherosclerosis* 2012;222:26-28.
15. Holden SE, Currie CJ. Do the benefits of analog insulin justify their costs? *Diabetes Management* 2012;2:173-5.
16. Holden SE, Poole CD, Morgan CL, Currie CJ. Evaluation of the incremental cost to the National Health Service of prescribing analogue insulin. *BMJ Open* 2011;1: e000258.

13.1.2. Conference proceedings

1. Holden SE, Jenkins-Jones S, Morgan CL, Schernthaner G, Currie CJ. Glucose-lowering with exogenous insulin monotherapy in type 2 diabetes: dose-response association with all-cause mortality, cardiovascular events, and incident cancer. Value In Health 2014;17:A240-A240.
2. Holden SE, Currie CJ. The impact of concomitant metformin on mortality and other serious outcomes in people with type 2 diabetes treated with insulin. Value In Health 2014;17:A241-A241.
3. Holden SE, Schernthaner G, Jenkins-Jones S, Currie CJ. Exogenous insulin and risk of all-cause mortality in type 2 diabetes: a dose-response association *Diabetologia* 2013;56:S96.
4. Holden SE, Setyawan J, Coghill D, Hodgkins P, Currie CJ. 1041 – The incidence, resource utilization and financial costs of treating children with attention deficit/hyperactivity disorder (ADHD) in the United Kingdom (UK). *Eur Psychiatry* 2013;28(Suppl 1):1

5. Poole CD, Currie CJ, Holden S, Singh A. Impact of disease severity on the total, health-related, financial costs of treatment of people with rheumatoid arthritis in the United Kingdom. *Value In Health* 2012;15:A36-A37.

13.2. Appendix 2 Rules for attributing the total international units represented by insulin prescriptions in CPRD

- If insulin presentation is a vial and quantity field = 10, then volume prescribed is assumed to be 100ml UNLESS ml or millilitres appears in text or pack type field where volume prescribed then = 10ml
- If insulin presentation is a vial and the quantity is a multiple of 10 and ≥20, the volume prescribed = quantity
- If the insulin presentation is cartridges, quantity is a multiple of 5, and the text or pack type is original pack (OP), then 1 OP = 1 cartridge or pen UNLESS text or pack type description indicates the number of boxes supplied. For example, if quantity = 5 and pack type description or text field indicates 5 boxes have been supplied then volume prescribed = 75ml or 37.5ml depending on cartridge size.
- If text or pack type field = millilitres or ml AND quantity = a multiple of the volume per unit for the insulin presentation in question, then the volume prescribed = quantity
- If the volume prescribed > 200ml, then volume prescribed is coded as missing
- Apply a default volume and year if only one insulin presentation was available after a specific date. For example:
- All Novo Nordisk penfills were assumed to be 3ml after 2003
- All Novo Nordisk pens were assumed to be 3ml after 1997
- All Humulin cartridges were assumed to be 3ml after 2000
- Where there was conflicting information in two or more of product name, pack type, text, and quantity fields, the volume prescribed was coded as missing

- If the origin of the insulin was not specified (as animal or human), the insulin was assumed to be of human origin.