EFFECTIVENESS OF SITAGLIPTIN VS SULPHONYLUREAS FOR MANAGING TYPE 2 DIABETES MELLITUS IN CLINICAL PRACTICE

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Declaration: I, Manuj Sharma confirm that the work presented in the thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis

Abstract

One challenging prescribing decision in type 2 diabetes mellitus (T2DM) is when clinicians must choose between sitagliptin and sulphonylureas as add-on to metformin based on effectiveness. Evidence on effectiveness of sitagliptin versus sulphonylureas as add-on to metformin was therefore systematically searched and revealed no study evaluating “real-world” comparative effectiveness of these treatments, particularly in older, more comorbid individuals. To address this gap, The Health Improvement Network, UK primary care database was used to extract a cohort of 26,844 individuals with T2DM prescribed these treatments and four cohort studies were undertaken to evaluate their comparative effectiveness.

The first two studies demonstrated no difference in HbA1c reduction, approximately 12 months after initiating either treatment as add-on to metformin, however a significant comparative weight reduction with sitagliptin in those aged 18-75 (-2.26kg 95%CI -2.48 to -2.04) and ≥75 (-1.31kg 95%CI -1.96 to -0.66) was found. Two further studies revealed individuals prescribed sitagliptin were 11% more likely to record an undesirable HbA1c >58mmol/mol (Hazard Ratio 1.11 95%CI 1.06-1.16), however nearly twice as likely to record an anti-diabetic treatment change (HR 1.98 95%CI 1.86-2.10) compared to sulphonylurea initiators. This analysis on treatment change also highlighted an underlying inertia in both groups, as 66.4% of those prescribed sitagliptin and 83.7% prescribed sulphonylureas had no treatment change introduced despite recording a HbA1c >58 mmol/mol.

This thesis provides “real-world” evidence that both sitagliptin and sulphonylureas are equally effective in lowering HbA1c and achieving glycaemic targets in a population that includes individuals aged ≥75 and with significant comorbidity. Sitagliptin is preferable for weight reduction. There is however, a substantial inertia in changing treatment when targets are not met, which is greater among sulphonylurea initiators. There remains a need to eliminate barriers preventing clinicians changing treatment when these two add-on medications prove inadequate, and further evaluate their longer-term comparative effectiveness.

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DISSEMINATED WORK FROM THIS THESIS

Three manuscripts have been published based on the work undertaken in this thesis. These manuscripts are based on the content presented in Chapters 2, 4 and 5 respectively and are cited below in the order they have been published. They are included in Appendix H for reference.

1. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ Open 2016; 6(1): e010210.

2. Sharma M, Petersen I, Nazareth I, Coton SJ. An algorithm for identification and classification of individuals with type 1 and type 2 diabetes mellitus in a large primary care database. Clin Epidemiol 2016; 8:373-80.

3. Sharma M, Beckley N, Nazareth I, Petersen I. Effectiveness of sitagliptin compared to sulfonylureas for type 2 diabetes mellitus inadequately controlled on metformin: a systematic review and meta-analysis. BMJ Open 2017; 7(10):e017260

Three further manuscripts based on Chapters 8, 9 and 10 are also being prepared.

I have also presented work from this thesis at national and international conferences. This has included 4 oral presentations given at each of the conferences below:

1. Society of Academic Care (SAPC) Annual Conference, Dublin 2016
2. International Society of Pharmacoepidemiology (ISPE) Annual Conference, Dublin 2016
3. International Society of Pharmacoepidemiology (ISPE) Annual Conference, Montreal 2017
4. European Association for the Study of Diabetes (EASD) Annual Conference, Lisbon 2017

Abbreviations

Abbreviation	Meaning
AACE/ACE	American Association of Clinical Endocrinologists
ACU	Acceptable Computer Usage
ADA	American Diabetes Association
AHD	Additional Health Data
AMR	Acceptable Mortality Rate
BMI	Body Mass Index
CASP	Critical Appraisal Skills Programme
CI	Confidence Interval
CrCl	Creatinine Clearance
DAG	Direct Acyclic Graph
DM	Diabetes Mellitus
DPP-4	Dipeptidyl-Peptidase-4
EASD	European Association for Study of Diabetes
F2FC	Face to Face Consultation Frequency
GPs	General Practitioners
HbA1c	Haemoglobin A1c
HR	Hazard Ratio
IDF	International Diabetes Federation
IRR	Incidence Rate Ratio
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OAD	Other Anti-diabetics
PR	Prevalence Ratio
RCT	Randomised Controlled Trial
Sita	Sitagliptin
SD	Standard deviation
Sulf	Sulphonylureas
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
THIN	The Health Improvement Network
UK	United Kingdom

Chapter 1 Background on Diabetes Mellitus

1.1 Chapter Overview

In this chapter, I will provide an overview of diabetes mellitus (both type 1 and type 2), their diagnoses and pharmacological management. I will focus, in particular on type 2 diabetes mellitus (T2DM) as this will be the diabetes subtype examined in this thesis. I will outline in particular, the specific treatment area within T2DM that will become the focus of this thesis before visiting it in greater depth in the systematic review in Chapter 2. This will then lead on to the specific aims and objectives for the thesis in Chapter 3.

1.2 What is Diabetes Mellitus?

Diabetes Mellitus (DM) is an endocrine disease associated with chronic hyperglycaemia due to relative deficiency in the hormone insulin, insulin resistance or sometimes both.[1] This disruption in the body's ability to regulate blood glucose levels leads to disturbances in carbohydrate, protein and fat metabolism.[1] This in turn can lead to severe, though often gradual, damage to many of the body's systems, in particular the cardiovascular system.[1]

Blood glucose levels are regulated closely in healthy individuals (3.5-8.0 mmol/L) despite the fact that an individual's demand may vary depending on level of activity and food consumed.[1] The hormone insulin is the main regulator of glucose metabolism although its actions are modified by other hormones such as glucagon and glucagon-like-peptide-1 (GLP-1) as well.[2] In a healthy individual that is fasting, insulin secretion from the pancreas triggers the release of stored glucose from the liver to raise blood levels.[1,2] In the post prandial state however, insulin promotes uptake of glucose by body cells to ensure blood levels do not get too high. Hence, this absence or resistance to insulin among diabetics can have several severe consequences which I will describe below. [1]

DM is an irreversible, progressive disease. Its global prevalence was estimated to be 9% among adults aged over 18 worldwide in 2014.[1] The World Health Organisation expects this prevalence to continue to rise and that DM will be among the top ten leading causes of death by 2030.[2]

There are two main forms of DM, type 1 and type 2 respectively, which together account for about 95% of all DM cases.[2] Other forms of DM include gestational diabetes (described below), while other rarer types including secondary forms of DM which may develop in response to other diseases and medication usage will not be detailed here.[1]

1.2.1 Type 1 Diabetes Mellitus

1.2.1.1 Clinical Features and Presentation

Type 1 diabetes mellitus (T1DM) is an autoimmune disease which peaks in incidence at puberty though it can manifest at any age. The generation of autoantibodies in the body which destroy pancreatic islet cells that produce insulin are largely responsible for the disease.[1] Both genetic links and environmental triggers have been identified as stimuli for the generation of these autoantibodies though the exact pathology for onset of disease still requires further elucidation.[1] The destruction of the pancreas leads to an absence of insulin to control blood glucose and hence these individuals are reliant on injections of insulin indefinitely to manage the disease.[3]

This form of DM is rapidly progressive and most commonly observed in children.[2] This is why it was previously known as juvenile onset diabetes, however latent forms of it have been observed to occur in later life.[1] The classical symptoms of DM associated with the presence of hyperglycaemia are nearly always present in newly presenting T1DM cases and include increasing thirst (polydipsia), frequency of urination (polyuria) and weight loss.[4] Approximately 25% of new diagnosis for T1DM in children are made as a result of hospital admission following an episode of severe hyperglycaemia known as diabetic ketoacidosis.[5,6] In a small number of cases, if this is left untreated, this can lead to a coma and even death.[7] In addition, where diagnosis is made late, there may already be symptoms of organ damage such as ocular disease, deafness, or other systemic complications.[8]

1.2.2 Type 2 Diabetes Mellitus

1.2.2.1 Clinical Features and Presentation

Type 2 diabetes mellitus (T2DM) is an acquired form of diabetes often associated with being overweight and having an unhealthy lifestyle with respect to diet and exercise.[9] It also shows a stronger association of onset with increasing age and is more common in certain ethnic groups such as South Asian and Afro-caribbeans.[10] Prevalence is highest amongst South Asians and Afro-Caribbeans settled in westernized countries further highlighting the importance of lifestyle in the development of this disease.

T2DM typically develops later in life and hence is sometimes referred to as maturity onset diabetes, though diagnoses of the disease are becoming common at younger ages possibly, in part, due to increasing childhood obesity.[11] T2DM has a slower rate of progression to severity, hence the majority of individuals are often diagnosed during routine screening and are often asymptomatic at diagnosis. Though the level of hyperglycaemia they experience may not be

sufficiently severe to manifest in symptoms, it is still capable of inducing longer term organ damage. These individuals do not require insulin immediately. However, depending on how well they manage the disease with lifestyle alterations and various non-insulin medications, they can often progress to needing insulin therapy at some stage in life.[12]

1.2.3 Gestational Diabetes

This is a form of DM that results in hyperglycaemia which is first detected during pregnancy. The diagnosis does not exclude the possibility that the onset of DM may have occurred prior to pregnancy and its name relates solely to the time of recognition. It applies regardless of whether the DM is managed with or without insulin.[13,14] Of women who have DM during pregnancy, it is estimated that approximately 87.5% have gestational diabetes (which may or may not resolve after pregnancy).[14] Diabetes in pregnancy is associated with risks to the woman and to the developing foetus and hence more liberal diagnostic criteria are applied to ensure it is identified and managed.[14]

1.3 Diagnosis of DM

1.3.1 Initial diagnosis of DM

As a manifestation of symptoms is not always the case, DM is primarily diagnosed on the basis of some form of measurement of blood glucose. Fasting plasma glucose and random plasma glucose have been used for several decades in the diagnosis of DM, however the use of glycated haemoglobin (HbA1c) for the diagnosis of DM was only introduced in 2011 (Table 1.1).[15] The HbA1c test which provides an indication of an individual's average blood glucose level for the past two to three months has been commonly used since 2011 for diagnosis. It measures the percentage of blood glucose attached to haemoglobin, the oxygen-carrying protein in red blood cells. The higher the blood glucose levels, the greater will be the percentage of haemoglobin with attached glucose and hence the higher the value of the HbA1c.[16]

Guidelines developed by the World Health Organisation (WHO) for the diagnosis of DM are shown in Table 1.1.[1] The plasma glucose thresholds are based on those found from studies to be sufficiently high to put an individual at risk of long term organ damage.

The WHO also define two pre-diabetic conditions which would place individuals at a higher risk of developing DM, impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).[1]

Table 1.1 Diagnosis of diabetes mellitus, gestational diabetes, impaired glucose tolerance and impaired fasting glucose

Condition	Parameter	Diagnostic Threshold
Diabetes Mellitus (Type 1 or Type 2)		
Symptoms plus	a) Random Venous Plasma Glucose or	≥ 11.1 mmol/l
	b) fasting plasma glucose (whole blood) or	≥ 7.0 mmol/l (≥ 6.1 mmol/l)
	c) two hour plasma glucose concentration or	≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT).
	d) HbA1c	≥ 48 mmol/mol (6.5%)
No symptoms plus	Two positive test results indicating diabetes mellitus (as above) BUT on separate days.	
Gestational Diabetes Mellitus		
	a) fasting plasma glucose or	≥ 5.6 mmol/l
	b) two hour plasma glucose concentration	≥ 7.8 mmol/l
Impaired Glucose Tolerance		
	a) fasting plasma glucose and	< 7.0 mmol/l
	b) two hour plasma glucose concentration	≥ 7.8 mmol/l and < 11.1mmol/l
Impaired Fasting Glucose		
	a) fasting plasma glucose and	6.1-6.9mmol/l
	b) two hour plasma glucose concentration	< 7.8 mmol/l

1.3.2 Classification of DM into type 1 and type 2

Once diagnosed with DM, the type of DM must be correctly identified as that will determine subsequent management particularly pharmacological treatment. In the majority of circumstances individuals with T1DM tend to be younger, slimmer and usually present symptomatically with a more severe and advanced form of the disease which requires insulin immediately for control.[17] A person is often diagnosed as having T2DM if he or she clearly does not have T1DM.[16]

Diagnosis is however, not always straightforward. There are an increasing number of individuals with T1DM, that may present with some residual insulin production and not require insulin immediately.[18] Equally, there are more severe cases of T2DM, appearing among younger age groups which may need insulin quite early in the disease trajectory and hence be misdiagnosed as T1DM.[19]

1.4 Complications of Diabetes Mellitus

Complications of DM are usually grouped into macrovascular and microvascular complications. Good glycaemic management in the early stages can prevent the occurrence of these complications.[8]

1.4.1 Macrovascular Complications

The risk of developing cardiovascular disease is more than doubled in individuals with DM and is the most common cause of death in this patient group. Cardiovascular disease is a broad spectrum of disorders of the heart and blood vessels and includes coronary heart disease, cerebrovascular disease, peripheral vascular disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism as well as myocardial infarction and stroke.[20] Peripheral vascular disease in particular, can cause significant pain, erectile dysfunction and foot complications associated with DM which can sometimes lead to limb amputations.

1.4.2 Microvascular Complications

Microvascular complications include diabetic retinopathy, nephropathy and neuropathy. Retinopathy is one of the major causes of blindness in the western world. There has been a greater focus on screening programmes for diabetic retinopathy in recent years as it is usually symptomless until more advanced. Diabetic nephropathy or kidney disease is another complication which can even require dialysis if renal function becomes severely compromised. Nerve damage or neuropathy can manifest differently depending on which parts of the nervous system become affected. Nerve damage can lead to pain but also to loss of sensation particularly in extremities such as the feet. Individuals often require medication to help manage some of these neuropathic complications.[21]

1.5 Management of Diabetes Mellitus

1.5.1 Management of T1DM

Guidance from the National Institute for Health and Care Excellence (NICE) recommends that an integrated package of care by a multi-disciplinary team be provided to all individuals diagnosed with T1DM. As part of this specialist advice on dietetic, lifestyle, mental health and footcare aspects should be provided.[17]

The cornerstone of managing T1DM involves the provision of insulin therapy. Insulin comes in several forms which differ in terms of duration of action and origin i.e. porcine, human etc. Insulin therapy must be tailored to a regimen that suits that individual which may involve anything from a

single injection to multiple injections daily. A continuous subcutaneous insulin infusion pump which secretes insulin gradually throughout the day is also available.[17]

1.5.2 Management of T2DM

Individualised dietetic and lifestyle advice is an essential first step following a diagnosis of T2DM, impaired glucose tolerance or impaired fasting glucose.[22] For some individuals, such alterations may be sufficient in managing the disease, however most will need some form of medication to help manage the condition.[22] Further details on types of medication available to manage T2DM are detailed below. Similar to T1DM a multi-disciplinary approach to managing the condition is essential.

1.6 Pharmacological Treatment of T2DM

1.6.1 Guidance on the management of T2DM

Unlike T1DM, the treatment options available for T2DM are extensive and pharmacologically diverse. The number of options has also increased significantly in the last decade with emergence of incretin-based therapies such as gliptins and GLP-1 (glucagon-line-peptide-1) analogues as well as SGLT-2 (sodium-glucose co-transporter-2) inhibitors. There is still limited effectiveness data for novel drug therapies in terms of longer-term control and the prevention of complications of T2DM, though cardiovascular outcome trials have now become a regulatory requirement for novel anti-diabetic treatments.[23] Periodic guidance from international bodies such as the American Diabetes Association (ADA) and European Association for Study of Diabetes (EASD) and national bodies such as the National Institute for Health and Care Excellence (NICE) have been very important in providing objective and detailed guidance to prescribers.[22,24]

1.6.2 Medications available in the UK to treat T2DM

1.6.2.1 Biguanides

Metformin is the only treatment in this class available in the UK. Its mechanism of action is poorly understood. It is thought metformin acts through potentiating insulin action through intracellular mechanisms and also decreasing hepatic glucose production. Metformin is recommended as the first line treatment of choice in T2DM for the majority of individuals regardless of level of obesity.[16,24] This is because it does not induce weight gain or hypoglycaemia. Hypoglycaemia refers to a blood glucose < 4mmol/mol and can be life threatening if not appropriately managed with immediate glucose intake.[22] The most common adverse effects of metformin are

gastrointestinal and include loss of appetite, nausea and diarrhoea. Lactic acidosis was previously a major concern though this fear has been somewhat allayed by recent studies.[25]

1.6.2.2 Sulphonylureas

There are several drugs of this class available in UK e.g. gliclazide, glipizide, glibenclamide, chlorpropamide, tolbutamide. They require functioning beta cells in the pancreas for effect as they stimulate them to increase insulin secretion. They are considered alternative first line agents to biguanides. However, as they cause weight gain and increase risk of hypoglycaemia they should be used with caution in at-risk groups.[16] They vary in their duration of action with longer-acting agents typically favoured where drug adherence is a problem while shorter-acting agents are favoured if there is a concern of hypoglycaemia. Other adverse effects such as blood dyscrasias are rare.

1.6.2.3 Gliptins

Gliptins also known as Dipeptidyl peptidase-4 inhibitors (DPP-4s) first became available in 2006 as another therapeutic option for use in T2DM. These agents reduce the breakdown of glucagon-like peptide 1 (GLP-1) by the enzyme dipeptidyly-peptidase-4. GLP-1 is secreted by cells of the small intestine in response to food intake and is important in triggering a cascade of biochemical activity that leads to increased insulin secretion. By preventing breakdown of GLP-1, gliptins allow it to exert its effect for a longer period and subsequently allowing for a more appropriate secretion of insulin in response to food intake.[26] The gliptins; sitagliptin, saxagliptin, linagliptin and vildagliptin are licensed for use as first line agents however NICE has generally recommended their use as second line therapy.[16,27] Sitagliptin is known to be the most widely used gliptin in the UK and was the first in its class to be licensed.[28] Gliptins are described as having no effect on weight (weight-neutral) and have a very low risk of inducing hypoglycaemia. A small, increased risk of pancreatitis has been reported with agents in this class.[29]

1.6.2.4 Thiazolidinediones

These agents such as pioglitazone and rosiglitazone activate a receptor called the peroxisome proliferator-activated receptor-ɣ (PPAR- ɣ) which can be found in adipose tissue, β-cells and throughout the vasculature. This activation results in enhanced insulin sensitivity and increase of glucose uptake by tissues in the body. NICE guidance recommends use of these agents mainly in combination with metformin or a sulphonylurea or as alternatives first line options to metformin.[16] Triple therapy with all three agents is sometimes used in individuals as an alternative

to insulin. These agents have been reported to increase the risk of weight gain, heart failure, anaemias and bone fractures.[30]

1.6.2.5 GLP-1 Mimetics

As detailed earlier, GLP-1 itself, is rapidly degraded in the body by the enzyme dipeptidyl peptidase 4 (DPP-4), however these synthetic drugs of GLP-1 are more resistant to degradation e.g. exenatide, liraglutide, dulaglutide.[31] These drugs can help induce weight loss, however they can cause nausea which can be sufficiently severe to lead to discontinuation of therapy. A risk of pancreatitis has also been attributed to this class of therapy though it appears to be rare.[29] NICE recommends their usage in particular as add on therapy in individuals who are overweight (BMI>35 kg/m2).[16]

1.6.2.6 Insulin therapy.

T2DM is a progressive illness, hence many individuals will ultimately need insulin therapy. Use of insulin can lead to significant weight gain and a risk of hypoglycaemia and hence physicians can be reluctant to introduce it early. Insulin is typically initiated as an adjunct to treatment with other agents, however some individuals may be entirely managed on insulin alone in a manner similar to T1DM. This is because certain individuals with T2DM, particularly those with lower BMI (< 25kg/m2) may have significant insulin deficiency as well as insulin resistance.[32] Doses of insulin required for T2DM may be substantially higher as the disease is caused by insulin resistance; whereas in T1DM the body cells still respond to standard insulin doses similar to those produced by a pancreas in healthy individuals. Regimens of insulin used may vary in a manner similar to T1DM with anything from single to multiple injections of insulin being used daily.[33]

1.6.2.7 Others

Other treatments for T2DM including meglitinides and α-glucosidase inhibitors such as acarbose are recommended by NICE to be reserved for individuals who are deemed unsuitable for management on more conventional treatments.[16] Sodium-glucose cotransporter-2 inhibitors (SGLT-2) were only recently licensed at commencement of this thesis. These will not be discussed in detail here.

1.6.3 Managing secondary complications of DM

In addition to treatments used to control blood glucose levels, several additional therapies are also utilised in individuals with DM to prevent and treat the complications of the disease. These include anti-hypertensive medicines, lipid lowering drugs, anti-thrombotic drugs as well as medication that may be provided to treat ocular problems, neuropathy, nephropathy as well as

gastric emptying.[16] This means that these individuals with T2DM can often be on quite complex medication regimens.

1.7 Challenges in prescribing in Type 2 Diabetes Mellitus

Given the multiple treatment options, now available to help manage the disease, pharmacological treatment of T2DM has become increasingly complex.[34,35] Metformin is recommended for use first line across all national and international guidelines.[16,24] However, thereafter prescribing becomes more difficult. Several options are available for use when metformin monotherapy fails, however two of the most common treatments prescribed are the gliptin, sitagliptin and sulphonylureas.[28,36] Though sitagliptin is only one of the drugs belonging to the gliptin class, it is well established as being the most common gliptin prescribed in the UK and US.[28]

1.7.1 Why Sitagliptin vs Sulphonylureas

The most recent guideline updates at time of commencement of this PhD work in 2015 from NICE, ADA and EASD did not discriminate between sitagliptin and sulphonylureas in terms of choice as add-on to metformin from an effectiveness point of view.[22,24] Other treatment options mentioned earlier such as GLP-1 analogues are more expensive, and clinicians, particularly those based in primary care, were still becoming more confident with their use so often the choice for second line comes down to a decision between sitagliptin or a sulphonylurea. Head to head, comparative effectiveness data comparing these two treatments as add-on to metformin is known to be limited.

1.8 Context of this chapter in overall work

I have shown in this chapter that the diagnosis and management of T2DM is challenging. Though T2DM does have some distinctive clinical features compared to T1DM, there is overlap in symptoms and treatment options. A vast number of pharmacological treatments are available for managing T2DM in particular, which though useful can make selection difficult. NICE and other international bodies provide objective guidance for use of these treatments to help guide physicians but some clinical decisions can be more challenging than others. One such challenging clinical scenario is choosing between use of sitagliptin or sulphonylureas for individuals with T2DM as an add-on to metformin, when metformin monotherapy has proved inadequate. This challenge will be explored further in this thesis.

In the next chapter, I will present a systematic review of the literature exploring effectiveness of sitagliptin compared to sulphonylureas among individuals with T2DM inadequately controlled on

metformin. Having reviewed this literature, I will then in Chapter 3 proceed to outline the specific aims and objectives as well as the structure of the remaining chapters in this thesis.

Chapter 2 Systematic Review

2.1 Chapter Overview

In this chapter, I will undertake a systematic review of the literature examining effectiveness of sitagliptin compared to sulphonylureas among individuals with type 2 diabetes mellitus (T2DM) as add-on to metformin. This review will help detail what is currently known with regards to this specific comparative effectiveness question and help identify gaps in evidence towards which I can target my work in this thesis.

2.2 Rationale for undertaking Systematic Review

Management of individuals with T2DM has become increasingly complex in recent years given the vast array of pharmacological treatments now available.[22,24] Gliptins and sulphonylureas represent two widely used classes of therapy, both of which act principally by ultimately increasing insulin secretion though their mechanisms of action are quite distinct. Sitagliptin is the most widely used gliptin in the US and UK, while alongside metformin, sulphonylureas such as gliclazide are the most widely prescribed oral anti-diabetic agent for T2DM.[28,37] An increasingly common challenge faced by clinicians involves deciding between use of sitagliptin or a sulphonylureas as potential options to add-on in individuals with T2DM inadequately controlled on metformin.

Clinical guidance from the American Association of Clinical Endocrinologists (AACE/ACE) recommends sitagliptin usage over sulphonylureas for second-line treatment,[38] however most other major international guidelines such as those from the UK National Institute for Heath and Care Excellence (NICE), American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD) and International Diabetes Federation (IDF) do not discriminate between these treatments and advocate that either may be selected as potential options to add-on, having accounted for patient preferences and medication safety.[22,24,39]

From a safety perspective, both sulphonylureas and sitagliptin have been studied in considerable depth. As this thesis will not be focusing on safety aspects, I will summarise this literature here. Firstly, a several fold higher risk of hypoglycaemia has been well established with sulphonylureas.[40,41] For instance, Krobot et al reported a substantially lower risk for both non-severe and severe hypoglycaemia when sitagliptin was added to metformin instead of a sulphonylurea: [HR: 0.05 (0.03 to 0.09) equating to 31 vs 448 events in 1172 trial participants].[42] This result has been found to be maintained across several vulnerable population groups including older adults in a subgroup analysis presented by Shankar et al,[43] who reported a

substantially lower rate of hypoglycaemia among 372 adults aged ≥ 65 years with sitagliptin compared to sulphonylureas (6.2% vs 27.8%). In fact, the recent cardiovascular outcomes trial undertaken with sitagliptin in 14,671 individuals led by Green et al, demonstrated no increased risk of hypoglycaemia when compared to placebo.[44] Secondly, an increased risk of pancreatitis with sitagliptin has also been reported and included in the product label.[27] However, several studies including the recent study by Green et al have failed to detect any such elevated risk indicating that if this risk is true, the increase is extremely low and thus far, been unquantifiable.[44,45] There have been conflicting reports regarding a worsening of symptomatic heart failure largely in individuals with pre-existing heart failure when prescribed sitagliptin, however Green et al did not report an increased risk, largely allaying this fear.[44,46]

Though the safety of both treatments has been extensively evaluated, from an effectiveness point of view, the advantages and disadvantages of either of the two are not as clear. Several randomized controlled trials have been conducted on both sitagliptin and sulphonylureas comparing them to placebo, however, these do not readily allow direct comparison between both treatments.

In this systematic review, I will collate and analyse evidence from both randomized controlled trials (RCTs) and observational studies to ascertain the effectiveness of sitagliptin compared to sulphonylureas in individuals inadequately controlled on metformin. I will examine a range of clinical outcomes for which data has been reported to ensure comprehensive coverage and understanding of the literature.

2.2.1 Objectives of the systematic review

The main objectives of the systematic review are

1. To review and summarise evidence from **randomised controlled trials** comparing the effectiveness of sitagliptin to sulphonylureas in individuals with T2DM inadequately controlled on metformin.
2. To review and summarise evidence from **observational studies** comparing the effectiveness of sitagliptin to sulphonylureas in individuals with T2DM inadequately controlled on metformin.

2.3 Methods

The full protocol for this systematic review was published online, on PROSPERO prior to undertaking this study and has been included in Appendix A (Supplementary Methods 2A1) for reference.[47]

2.2.1 PICO (Population, Intervention, Comparator, Outcome) Criteria

Population: Individuals with type 2 diabetes mellitus inadequately controlled on metformin

Intervention: Sitagliptin

Comparator: Sulphonylureas (gliclazide, glipizide, glibenclamide, tolbutamide, chlorpropamide, glimepiride)

Outcomes:

1. Change in HbA1c from baseline (mmol/mol)
2. Number achieving HbA1C at study end < 53mmol/mol (< 7%)
3. Number achieving HbA1C at study end < 48mmol/mol (< 6.5%)
4. Change in fasting plasma glucose from baseline (mmol/l)
5. Change in weight from baseline (kg)
6. Change in BMI (Body Mass Index) from baseline (kg/m^2)
7. Change in blood pressure from baseline (mmHg)
8. Change in cholesterol from baseline (mmol/mol)
9. Other effectiveness outcomes relating to reduction in onset of complications of diabetes e.g. nephropathy, neuropathy, retinopathy, onset of cardiovascular disease, occurrence of cardiovascular events e.g. myocardial infarction, stroke
10. Any longer-term effectiveness outcomes i.e. follow-up of greater than 2 years

2.3.2 Search Strategy and Study Selection

Eligible studies of any language were identified using electronic searches for randomised controlled trials, observational studies and conference abstracts using MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to June 1 2016 and EMBASE (January 1 1980 to June 1 2016). I developed search strategies for individual databases and had them reviewed by an information specialist in the area to ensure rigour. These search strategies have been included in full in Appendix A (Supplementary Methods 2A2-2A4). Additional studies and grey literature were retrieved by screening references of retrieved studies and by searching International Pharmacy Abstracts, conference proceedings on Scopus and the World Health Organisation international clinical trial registry. I also contacted manufacturers directly in cases where data required was not available in the public domain, however no additional data was made available.

I aimed to identify all phase 3 RCTs and observational studies conducted post-marketing authorisation comparing sitagliptin with sulphonylureas (gliclazide, glipizide, glibenclamide, tolbutamide, chlorpropamide, glimepiride) in adults with T2DM inadequately controlled on metformin. I required that studies have a minimum of 1 month patient follow-up after initiation with sitagliptin or sulphonylureas (however, a minimum of 3 months was required for reported changes in HbA1c).

I performed the full search strategy, removed duplicates and selected the articles. The second reviewer (Nicholas Beckley – hereafter abbreviated as NB) independently analysed the selections for eligibility of inclusion. Studies were screened based on title and abstract initially, following which full texts were obtained and assessed for inclusion. All records identified in searches were managed and stored in a reference management software (EndNote X7®, Thomson Reuters, New York, NY, USA).

2.3.3 Data Extraction

Data extraction from identified studies and appraisal of individual studies was conducted by both myself and the additional reviewer (NB) independently. As per guidance from the Cochrane Collaboration, independent study identification, data extraction and study appraisal is important in order to deem a review to be systematic.[48]

All data was extracted independently by myself as well as a second reviewer (NB) into standardised forms and entered into Microsoft Excel®. Data extracted included study details, participant details, intervention details (drug name, dose, frequency). The intention to treat populations were used for analysis where possible. The primary outcome examined the change from baseline in HbA1c (mmol/mol) between sitagliptin and sulphonylurea groups. Secondary outcomes examined the number achieving HbA1c at study end of < 53mmol/mol (< 7%) and < 48mmol/mol (< 6.5%), change from baseline in fasting plasma glucose (mmol/mol), weight (kg), BMI (kg/m^2), systolic and diastolic blood pressure (mmHg), total cholesterol (mmol/mol) and triglycerides (mmol/mol) between sitagliptin and sulphonylurea groups. In addition, all data on longer-term effectiveness outcomes where reported was also extracted. This included data examining the risk of insulin initiation after commencement of sitagliptin compared to sulphonylureas as well as time before a change in treatment was needed. Though my systematic review protocol included plans to extract data on longer-term outcomes such as examining risk of macrovascular and microvascular complications of diabetes such as nephropathy, neuropathy, retinopathy, incidence of cardiovascular events e.g. myocardial infarction, stroke when reported,

no such data was retrieved. All disagreements between the two reviewers were resolved by consensus or discussion when needed.

2.3.4 Critical Appraisal and Assessment of studies retrieved

The risk of bias assessments for randomised controlled trials and appraisal using the Newcastle Ottawa scale for observational studies were carried out by both myself and second reviewer (NB) independently and checked for agreement. Differences were resolved through consensus. I also appraised each study in further detail using the Clinical Appraisal Skills Programme (CASP) tool, which has been included in Appendix A for reference (Supplementary Appraisal 2A1).[49]

2.3.4.1 Risk of Bias Assessment of RCTs

The Cochrane Collaborations Risk of Bias Tool was used to assess heterogeneity and quality for the RCTs. This tool was developed by a team of statisticians and epidemiologists and is recommended by Cochrane for use in systematic reviews and meta-analysis.[48] All six domains in the risk of bias tool were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting. Each domain was graded as a) Low bias b) Unclear bias or c) High bias as outlined in Table 2.1.[48]

Table 2.1 Cochrane Collaboration's tool for assessing risk of Bias adapted from the Cochrane Handbook.[48]

Bias Domain	Source of Bias	Interpretation
Selection Bias	Sequence generation	Was the allocation sequence adequately generated?
Selection Bias	Concealment	Could intervention allocation have been foreseen before/during enrolment?
Performance Bias	Blinding of participants/personnel	Were measures used to blind them from the allocated intervention adequately?
Detection Bias	Blinding of outcome assessment	Were measures used to blind them from the allocated intervention adequately?
Attrition Bias	Incomplete outcome data	Were incomplete outcome data adequately addressed/ withdrawals/dropouts accounted for?
Reporting Bias	Selective outcome reporting	Are reports of the study free of suggestion of selective outcome reporting?
Other Bias	Anything else	Was the study apparently free of other problems that could put it at a high risk of bias?

2.3.4.2 Newcastle Ottawa Scale for appraisal of Observational Studies

The methodological quality of the observational studies included was assessed using the Newcastle-Ottawa quality assessment scales.[50] This scale consists of a “star-rating system” in which a study is judged on three broad domains: the selection of the study groups; the comparability of the groups; and the ascertainment of either the exposure or outcome of interest

for observational studies respectively.[50] An example of a checklist for use of the Newcastle Ottawa Scale in cohort studies is included in Appendix A (Supplementary Methods 2A5).

2.3.4.3 Critical Appraisal Skills Programme (CASP) RCT critical appraisal checklist

Each study deemed eligible for inclusion was also independently critically appraised by myself using the CASP RCT and observational study critical appraisal checklist.[49] This tool has been assembled by several academic experts, piloted and tested before being made available for use by others. It provides a useful aid for reviewers when critiquing research by helping ensure they focus on issues which are most fundamental to determining study quality.[49] Use of this tool also served as a means of gathering data needed for appraisal that was not included as part of the Cochrane risk of bias or Newcastle-Ottawa Scale assessments described above.

2.3.5 Data synthesis and Statistical Analysis

I undertook all data synthesis. Weighted mean differences were calculated for continuous outcomes and odds ratios or hazard ratios for all dichotomous outcomes where possible. I planned to conduct meta-analyses if included articles were of sufficiently comparable quality and homogenous in outcomes. Forest plots were constructed and an overall descriptive analysis was undertaken examining each outcome across the studies where reported with a comprehensive account of study quality.

Given the breadth of research methods identified, the significant variation in duration of follow-up across the studies and the overlapping patient populations in several of the studies retrieved; a meta-analysis including all studies was not deemed appropriate. However, as part of my subgroup study analysis, I did undertake a meta-analysis for outcomes where two or more studies were available of a sufficiently homogenous design and standard. Data synthesis was undertaken using a fixed-effects model (Mantel-Haenszel method) unless our assessment of study qualities determined a fixed-effects model was unsuitable or significant heterogeneity was evident.[51] Heterogeneity was assessed using the I^2 statistic, with an I^2 statistic greater than 50% considered indicative of significant heterogeneity and necessitating use of a random-effects model (Dersimonian-Laird method) for meta-analysis.[48,52] Sensitivity analysis was undertaken to examine impact of duration of study follow-up on results, however no change was observed. All analysis was undertaken using STATA statistical software package (Version 13®).

2.4 Results

2.4.1 Search Results and Study Characteristics

The process by which the final 12 studies for inclusion were selected is depicted in Figure 2.1. The majority of studies for which full text was reviewed were excluded because they used an unsuitable comparator e.g. placebo or a medication other than sulphonylureas. A more detailed rationale behind exclusion of each individual study based on full text review is included in Appendix A (Supplementary Table 2A1).

Included studies consisted of seven randomized controlled trials (RCTs),[40,53-58] and five observational studies (Table 2.2).[59-63] Among the RCTs, four studies used glimepiride exclusively as the sulphonylurea comparator.[40,53,54,58] Two studies exclusively used glipizide,[56,57] while one study used glibenclamide.[55] Among the observational studies, a range of sulphonylureas were used as comparators. Duration of patient follow-up in the RCTs ranged from one month for the shortest,[54] to 24 months for the longest studies.[53,57] Duration of patient follow-up was in general, longer in the observational studies ranging from three months in the shortest prospective cohort study,[62] to 72 months in the longest.[60] Four of the seven RCTs required individuals to be on metformin at a dose of ≥ 1500mg at baseline, [40,53,56,57] while this was not required for any of the observational studies (Table 2.2). Further details on study exclusion criteria across the studies can be found in Table 2.3.

The characteristics of participants across the studies are summarized in Table 2.4. The study population ranged from 34 individuals in the smallest RCT,[54] to 1,172 in the largest.[57] Observational study sizes ranged from 69 participants to 20,529 individuals in the largest cohort study.[60,61] The mean age of participants ranged from 54.3 years to 59.6 years in the RCTs and 46.9 years to 64.2 years in the observational studies. The mean baseline HbA1c ranged from 53 mmol/mol to 67 mmol/mol in the RCT while it ranged from 58 mmol/mol to 72 mmol/mol across the observational studies. Mean weight at baseline ranged from 80.6 kg to 91.8 kg in the RCTs while it ranged from 63.8 kg to 74.5 kg in the observational studies. However, weight was often poorly reported.

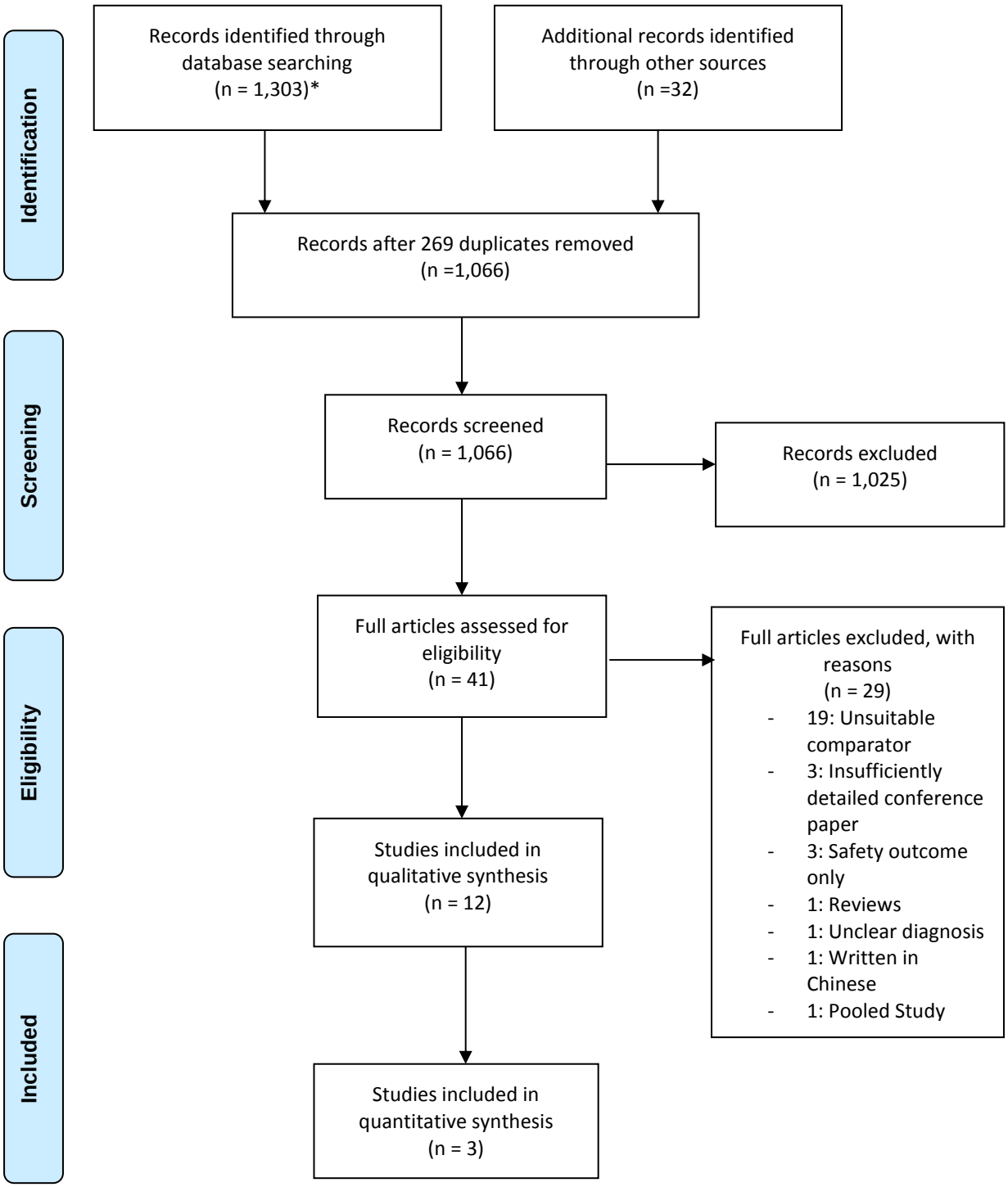


Figure 2.1 PRISMA Flow diagram for study identification, selection and exclusions
*Monthly automated alerts from 01/11/15 to 01/06/16 consisting of updates to the search strategy identified additional articles in Embase, Medline and CENTRAL that have been included in the flow diagram above. However, no eligible studies for inclusion were obtained through these updates. (Figure taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 3).

Table 2.2 Characteristics of the included studies

Study	Type	Sita Dose	Sulf Dose	Duration†	Inclusion Criteria	Primary Outcome
Ahren et al§ (2014)	RCT	100mg	Glim 2-4mg	24	Aged ≥18 years and T2DM with baseline HbA1c ≥53mmol/mol and ≤86mmol/mol and prescribed metformin ≥1,500 mg or maximum tolerated dose, BMI 20-45 kg/m2, creatinine clearance >60mL/min, normal thyroid-stimulating hormone concentration or clinically euthyroid.	Change in HbA1C from baseline
Arech. et al (2010)	RCT	100mg	Glim 1-6mg	7.5	Aged ≥18 years and T2DM with baseline HbA1c ≥48mmol/mol and ≤75mmol/mol and prescribed metformin ≥1,500 mg/day	Change in HbA1C from baseline
Kim et al (2013)	RCT	100mg	Glim 2mg	1	Aged 18–80 years and T2DM for <10 years with baseline HbA1c ≥53mmol/mol and ≤86mmol/mol prescribed metformin and BMI 20–30kg/m^2	Change in HbA1C from baseline
Koren et al (2012)	RCT	100mg	Glib 5mg	3	Aged 18–75 years and T2DM with baseline HbA1c ≥53mmol/mol and prescribed metformin.	Change in arterial stiffness from baseline
Nauck et al (2007)	RCT	100mg	Glip 5-20mg	12	Aged 18-78 years and T2DM with baseline HbA1c ≥48mmol/mol and ≤86mmol/mol and prescribed metformin ≥1,500 mg/day	Change in HbA1C from baseline
Seck et al¥ (2010)	RCT	100mg	Glip 5-20mg	24	Aged 18-78 years and T2DM with baseline HbA1c ≥48mmol/mol and ≤86mmol/mol and prescribed metformin ≥1,500 mg/day	Change in HbA1C from baseline
Sriva. et al (2012)	RCT	50-200mg	Glim 1-4mg	4.5	Aged ≥18 years and T2DM with baseline HbA1c ≥53mmol/mol and ≤86mmol/mol and prescribed metformin	Change in HbA1C from baseline
Derosa et al(2015)	Prosp. Cohort	100mg	Var*	60	Aged >18 and T2DM with baseline HbA1c ≥64mmol/mol, prescribed metformin and BMI 25-30 kg/m^2	Change in HbA1C from baseline
Inzuc. et al (2015)	Retro. Cohort	Var	Var*	72	Aged ≥18 years and T2DM, having initiated therapy with metformin in the 12 months preceding the index date on which sitagliptin or sulphonylurea were initiated	Risk of insulin initiation
Ki Lee et al (2013)	Prosp. Cohort	100mg	Var*	6	Aged ≥18 years and T2DM with a baseline HbA1c level ≥58mmol/mol prescribed metformin	Change in HbA1C from baseline
Suraj et al (2015)	Prosp. Cohort	100mg	Var*	3	Aged 18–70 years with T2DM and a baseline HbA1c ≥53mmol/mol and prescribed metformin	Change in HbA1C from baseline
Valen. et al (2015)	Prosp. Cohort	100mg	Var*	36	Aged ≥18 years and prescribed metformin with inadequately controlled T2DM as determined by physician judgement	Risk of need for treatment change

§Only sitagliptin and sulphonylurea arms in RCT considered
*Use of any sulphonylurea was permitted. In Suraj et al, glibenclamide 5mg, glimepiride 1mg or gliclazide 60mg were permitted only.
†Duration reported in months
¥Seck et al is an extended follow-up study of Nauck et al, only Seck et al was included for meta-analysis
Sita=sitagliptin, Sulf=sulphonylureas, RCT=randomized controlled trials, Prosp=prospective, Retro=retrospective, Glim=glimepiride, Glib=glibenclamide, Glip=glipizide, HbA1c=haemoglobin A1c, BMI=body mass index.
Note: Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 3).

Table 2.3 Major exclusion criteria across included studies

Author & Publication date	Major Exclusion Criteria
Ahren et al (2014)	Type 1 Diabetes, pregnancy, current symptomatic heart failure (NYHA Class III or IV), symptomatic biliary disease or history of pancreatitis, recent clinically significant cardiovascular and/or cerebrovascular disease (≤2 months before screening), treated gastroparesis, history of GI surgery thought to significantly affect upper GI function, history of most cancers not in remission for at least 3 years, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, resting systolic blood pressure >160 mmHg and/or diastolic blood pressure >100 mmHg, lipase above the upper limit of normal (ULN), haemoglobinopathy that could affect HbA1c, and alanine aminotransferase or aspartate aminotransferase more than 2.5 times the ULN
Arech. et al (2010)	Type 1 Diabetes, used any anti-diabetic besides metformin within 12 weeks of screening, had renal function impairment prohibiting the use of metformin or had a fasting blood glucose of <6.1 or >13.3 mmol/l at randomization.
Kim et al (2013)	Major hepatopathy, ischemic heart disease or cerebrovascular disease or a history of such disease, a creatinine level > 0.133mmol/L, treatment with agents other than metformin or other medicine that might influence blood glucose and steroid levels, and major diabetes complications (chronic renal insufficiency, proliferative retinopathy, stroke).
Koren et al (2012)	Creatinine clearance < 30mL/min, a history of treatment with gliptins, GLP-1 analogues or sulphonylureas during the last 3 months, treatment with nitrates, uncontrolled heart failure, uncontrolled hypertension, and/or any change in the hypertensive medications within 1 month prior to starting the study, malignancy, and pregnancy.
Nauck et al (2007)	Type 1 Diabetes, renal impairment, insulin use within 8 weeks of screening, Fasting Plasma Glucose >15mmol/l, and if on non-stable doses of lipid lowering, anti-hypertensive, thyroid medications, hormone replacement therapy or birth control medication.
Seck et al (2010)	Type 1 Diabetes, renal impairment, insulin use within 8 weeks of screening, Fasting Plasma Glucose >15mmol/l, and if on non-stable doses of lipid lowering, anti-hypertensive, thyroid medications, hormone replacement therapy or birth control medication.
Sriva. et al (2012)	Type 1 Diabetes, evidence of cardiac failure, evidence of hepatic or renal insufficiency or other terminal illnesses.
Derosa et al(2015)	Patients with a history of ketoacidosis, unstable or rapidly progressive diabetic retinopathy,nephropathy, neuropathy, impaired hepatic function, impaired renal function, severe anaemia, New York Heart Association class I–IV congestive heart failure, history of myocardial infarction or stroke, cerebrovascular conditions within 6 months before study enrolment, history of cancer and pancreatitis.
Inzuc. et al (2015)	Type 1 Diabetes, gestational or secondary diabetes, non-metformin anti-diabetic use and no prescription for other oral anti-diabetics in the first 90 days after the index date.
Ki lee et al (2013)	Recent (≤6 months) history of a major cardiovascular event, current hepatic, renal, haematologic, or gastrointestinal disease or those that had undergone systemic corticosteroid treatment in the previous 12 weeks.
Suraj et al (2015)	Type 1 Diabetes, on insulin, with secondary diabetes, experiencing complications on or during treatment plan, known or suspected hypersensitivity to study drugs, co-morbid illness such as cardiovascular disease, renal failure and liver disease.
Valen. et al (2015)	No exclusion criteria specified

Note: RCTs are listed alphabetically above dividing line and observational studies are listed alphabetically below dividing line.
Note 2:Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 3).

Table 2.4 Individual characteristics across the included studies

Study	Participants		Age (SD)		Male n(%)		Diabetes duration years (SD)		HbA1c % (SD) [mmol/mol, SD)		FPG mmol/l (SD)		Weight kg (SD)	
	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf
Ahren et al (2014)	302	307	54.3 (9.8)	54.4 (10.0)	139 (46.0)	158 (51.5)	5.8 (4.8)	6.0 (4.8)	8.1 (0.8) [65, 8.7]	8.1 (0.8) [65, 8.7]	9.2 (2.6)	9.3 (2.5)	90.3 (19.1)	91.8 (20.4)
Arech. et al (2010)	516	519	56.3 (9.7)	56.2 (10.1)	284 (55.0)	279 (53.8)	6.8 (4.6)	6.7 (4.8)	7.5 (0.7) [58, 7.7]	7.5 (0.8) [58, 8.7]	8.0 (1.8)	8.1 (19)	80.6 (15.2)	82.0 (16.7)
Kim et al (2013)	17	17	59.6 (6.7)	55.8 (6.6)	12 (75.0)	7 (41.2)	4.8 (5.2)	5.9 (4.2)	7.0 (0.5) [53, 5.5]	7.3 (0.4) [56, 4.4]	7.3 (0.5)	8.7 (0.7)	NR	NR
Koren et al§ (2012)	40	40	59.0(10.0)	59.0(10.0)	25(62.5)	25(62.5)	7.8(5.0)	7.8 (5.0)	8.3 (1.1) [67, 12]	8.3 (1.1) [67, 12]	9.4 (0.7)	9.4 (0.7)	NR	NR
Nauck et al (2007)	588	584	56.8(9.3)	56.6 (9.8)	336 (57.1)	358 (61.3)	6.5 (6.1)	6.2 (5.4)	7.7 (0.9) [61, 9.8]	7.6 (0.9) [60, 9.8]	9.2 (2.3)	9.1 (2.3)	89.5 (17.4)	89.7 (17.5)
Seck et al† (2010)	588	584	56.8(9.3)	56.6 (9.8)	336 (57.1)	358 (61.3)	6.5 (6.1)	6.2 (5.4)	7.7 (0.9) [61, 9.8]	7.6 (0.9) [60, 9.8]	9.2 (2.3)	9.1 (2.3)	89.5 (17.4)	89.7 (17.5)
Sriva. et al (2012)	25	25	NR	NR	NR	NR	NR	NR	8.3 (0.4) [67, 4.4]	8.2 (0.6) [66, 6.6]	10.2 (0.6)	9.9 (0.7)	NR	NR
Derosa et al(2015)	216	NR¥	NR	NR	NR	NR	NR	NR	8.3 (0.3) [67, 3.3]	8.5 (0.5) [69, 5.5]	8.1 (0.8)	8.3 (0.9)	NR	NR
Inzuc. et al (2015)	6104	14425	57.4 (11.8)	58.0 (12.5)	3074 (50.4)	7504 (52.0)	NR	NR	7.9 (1.6) [63, 17.5]	8.4 (2.0) [68, 21.9]	NR	NR	NR	NR
Ki Lee et al (2013)	38	31	50.2 (13.7)	54.8 (11.6)	24 (63.2)	16 (51.6)	1(0,6)*	1(0,12)*	9.4 (7.9,11.1)* [79 (63,98]	8.9 (8.2,10.2)* [74 (66,88)]	9.6 (7.5,11.3)*	9.3 (7.7,10.8)*	74.5 (11.6)	69.9 (15.4)
Suraj et al (2015)	50	50	46.9 (9.6)	48.9 (9.3)	34 (68.0)	19 (38.0)	3.4(3.5)	2.8(3.0)	8.2 (1.0) [66, 10.9]	8.7 (1.4) [72, 15.3]	10.2 (3.2)	10.8 (3.4)	65 (12.2)	63.8 (9.7)
Valen. et al (2015)	1874	733	62.4 (10.8)	64.2 (11.5)	1108 (59.4)	422 (57.6)	6.4 (5.9)	7.0 (5.6)	7.5 (1.0) [58, 10.9]	7.6 (1.0) [60, 10.9]	8.6(2.1)	8.5(2.2)	NR	NR

§Crossover Trial hence characteristics same in both arms

¥In Derosa et al, the authors compared several groups of individuals prescribed metformin (metformin and sulphonylureas, metformin and pioglitazone) and did not detail how many were in the metformin and sulphonylureas group specifically.

*Median and Interquartile range reported (not mean)

† Seck et al is an extended follow-up study of Nauck et al, only Seck et al was included for meta-analysis

Sita=sitagliptin, Sulf=sulphonylureas, NR=not reported, SD=standard deviation, HbA1c=haemoglobin A1c, FPG=fasting plasma glucose.

Note: RCTs are listed alphabetically above dividing line and observational studies are listed alphabetically below dividing line.

Note 2: Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 3).

2.4.2 Critical Appraisal and Assessment of studies retrieved

For each study identified for inclusion in this systematic review, I appraised the study in detail using the CASP review tool. Each individual study appraisal is included in Appendix A for reference (Supplementary Appraisal 2A1). Below, I summarise the findings from this appraisal

2.4.2.1 Risk of Bias Assessment for Randomized Controlled Trials

Out of 7 RCTs, 3 studies were judged to be at high risk of bias in one of the 7 domains examined as shown in Table 2.5. A lack of blinding of participants and personnel put both Srivastava et al and Koren et al at high risk of bias.[55,58] Additionally, Koren et al was also deemed to be at high risk of selection bias due to the absence of adequate randomization of participants.[55] Kim et al was at high risk of reporting bias as all outcomes e.g. change in HbA1c were reported in absolute terms without adjustment (despite imbalance in gender and baseline fasting plasma glucose after randomization) and no comparative analysis examining both treatments was undertaken.[54] In this study, it was also unclear whether sequence generation for randomization was inadequate or baseline imbalances was simply due to the small sample size for the study of 34.[54] This lack of adjustment in analysis meant any results presented by Kim et al could not be used for analysis. Risk of other bias was also high for Srivastava et al due to an absence of presentation of baseline characteristics of study participants which made the final study results (especially given the small sample size of 25 in each arm) challenging to interpret. [58]

2.4.2.2 Assessment of study quality of observational studies using Newcastle Ottawa Scale

Based on use of the Newcastle Ottawa Scale described earlier, 2 of our 5 observational studies were deemed to be of low quality as shown in Table 2.6. Suraj et al achieved a low quality rating as it did not meet the standard expected for cohort comparability mainly due to a failure to adjust for confounders such as age, sex, baseline HbA1c, weight, and metformin dose in the final analysis.[62] Derosa et al achieved a low quality rating as they had a strict cohort study exclusion criteria excluding individuals with more poorly controlled T2DM. Though they matched for age, sex and diabetes duration they failed to adjust for other potentially relevant confounders such as metformin dose.[59] Derosa et al also had significant loss to follow-up but failed to describe it sufficiently clearly and discuss if this may have biased the results.[59] Further details on methodological approaches used to control for confounding in each of the 5 observational studies which helped assign the appropriate star rating is provided in Table 2.7.

Table 2.5 Risk of Bias Assessment across Randomised Controlled Trials

RCT Study Bias Domain	Selection Bias	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other
	Sequence generation	Allocation Concealment	Blinded to Participants/ personnel	Blinded to Outcome Assessors	Incomplete outcome data	Selective outcome reporting	Other bias
Ahren et al	Unc	Unc	Low	Low	Low	Low	Low
Arechavaleta et al	Low	Low	Low	Low	Unc	Low	Low
Kim et al	Unc	Unc	Low	Low	Low	High	Low
Koren et al	High	High	High	Low	Low	Low	Low
Nauck et al	Low	Low	Low	Low	Low	Low	Low
Seck et al	Low	Low	Low	Low	Unc	Low	Low
Srivastava et al	Low	Low	High	Low	Unc	Unc	High

High=High risk of Bias in RCT (red), Unc=Unclear risk of bias in study (yellow), Low=Low risk of bias in study (green).
Note: Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 3).

Table 2.6 Quality Assessment of observational studies using Newcastle Ottawa Scale

Observational Study	Study Design	Selection (Out of 4)	Comparability (Out of 2)	Outcome (Out of 3)	Evidence Quality (low/moderate/high)
Derosa et al	Prospective Cohort	* * *	*	* *	Low
Inzucchi et al	Retrospective Cohort	* * * *	* *	* * *	High
Ki lee et al	Prospective Cohort	* * *	* *	* *	Moderate
Suraj et al	Prospective Cohort	* * * *		*	Low
Valensi et al	Prospective Cohort	* * * *	* *	* * *	High

Note: Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 3).

Table 2.7 Analysis approaches and methods used to control confounding across included observational studies

Observational Study	Study Design	Analysis Approach	Confounders Accounted for	Potential Confounders Not Accounted for
Derosa et al	Prospective Cohort	Matched analysis for age, sex and diabetes duration. Strict inclusion criteria and though limited data provided on baseline characteristics, the groups were well matched for characteristics reported.	Age, sex, diabetes as discussed	There are a multitude of additional variables that the authors could have considered that could introduce confounding relating to diet, socioeconomic status, concomitant medication and comorbidities.
Inzucchi et al	Retrospective Cohort	The authors incorporate several design features to minimise bias and account for confounders 1. Large sample size from large database 2. Propensity Score matching analysis to ensure more accurate comparison. 3. Appropriate prespecified sensitivity analysis conducted exploring impact of missing data and subgroups	Propensity score matching created 3,864 matched pairs with no significant differences in baseline characteristics across a wide range of baseline demographic, geographical, laboratory measurements as well as comorbidities.	Nil of note.
Ki lee et al	Prospective Cohort	Strict inclusion criteria meant that despite lack of randomization, no significant difference was evident in baseline characteristics reported.	No confounders adjusted for in analysis, however have demonstrated that baseline characteristics were highly similar for demographic and anthropometric characteristics	There are a multitude of additional variables that the authors could have considered that could introduce confounding relating to diet, socioeconomic status, concomitant medication and comorbidities. However, most comorbid individual were excluded from the studies through the strict exclusion criteria.

Observational Study	Study Design	Analysis Approach	Confounders Accounted for	Potential Confounders Not Accounted for
Suraj et al	Prospective Cohort	Several differences were evident in baseline characteristics including imbalances across gender, fasting plasma glucose, diabetes duration. However, no adjustments were made in final analysis	No adjustments made to account for confounding in final analysis	The authors did not present any adjustments even for demographic variables such as age, sex, HbA1c and metformin dose. In addition there may have been other relevant confounders too such as concomitant medications and certain comorbidities as well (though some of these individuals may have been excluded due to the exclusion criteria).
Valensi et al	Prospective Cohort	The authors incorporate several design features to minimise bias and account for confounders 1. Physicians were asked to enrol individuals that were deemed by their judgement equally eligible for sitagliptin or sulphonylureas 2. Propensity Score was generated using a broad range of demographic, clinical measures e.g. HbA1c etc., comorbidity and treatment confounders and used to adjust final analysis 3. Time varying confounders which may have introduced bias after study initiation were also analysed 4. Several sensitivity analyses were conducted exploring impact of missing data and reported in manuscript appendix in detail	Propensity score calculated across an extensive range of potential confounding characteristics and used to adjust final analysis	Nil of note.

Note:Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 3).

2.4.3 Outcomes

Meta-analysis was feasible for 3 studies across 5 outcomes: Ahren et al, Arechavaleta et al and Seck et al.[40,53,57] These studies were chosen as they were of high quality and all exceeded a follow-up period of 6 months in duration. A fourth study, led by Nauck et al could not be included for meta-analysis,[56] as Seck et al was an extended follow-up of this study and this would have led to double counting of individuals. The remaining studies reported on were included for qualitative description and to allow comparison.

2.4.4 Glycaemic change

In total, 7 studies reported glycaemic change (Figure 2.2A) and I performed meta-analysis for 3 of these RCTs as detailed earlier.

Compared to sulphonylureas, treatment with sitagliptin produced a similar glycaemic change, as measured by reductions in HbA1c from baseline: [Weighted Mean Difference (WMD) in HbA1c 0.54 mmol/mol 95% confidence interval (CI) -0.28 to 1.35; I^2=0%)] (graph in HbA1c units of % included in Appendix A - Supplementary Figure 2A1). There was no significant different in the odds for achieving a HbA1c of < 53mmol/mol by the end of the study between sitagliptin and sulphonylureas [Odds Ratio (OR) 0.98 95% CI 0.85 to 1.13, I^2=0%)] (Figure 2.2D). In the study led by Srivastava et al, sulphonylureas were shown to be superior to sitagliptin for HbA1c reduction; [Mean Difference (MD) in HbA1c 5.80 mmol/mol 95% CI 4.67 to 6.93].[58] However, study follow-up was shorter (4.5 months) and this study by Srivastava et al did not meet the quality requirements to be included in the meta-analysis.[58]

In the observational studies, glycaemic change was also reported in the study led by Suraj et al where a significantly greater reduction in HbA1c was observed with sulphonylureas (MD 5.30mmol/mol 95% CI 2.07 to 8.53), (Figure 2.2A).[62] Derosa et al reported a change from baseline in HbA1c after 5 years in a prospective cohort study,[59] however they did not adjust for relevant confounders which made their results difficult to interpret and hence I have not presented them.

2.4.5 Weight Change

Meta-analysis of the three RCTs detailed earlier, showed statistically significant comparative reduction in weight with sitagliptin from baseline compared to sulphonylureas (WMD -2.05kg 95% CI -2.38 to -1.71; I^2=0%) (Figure 2.2B). This weight difference was driven by an approximate 1kg weight loss with sitagliptin initiators and 1kg weight gain with sulphonylurea initiators. Treatment with sitagliptin also showed significant reduction in weight in the remaining RCTs as shown in

(Figure 2.2B). The greatest comparative weight reduction was observed in the 12 month RCT led by Nauck et al (MD -2.60kg 95% CI -3.31 to -1.89).[56]

The prospective cohort study led by Suraj et al also revealed a similar weight reduction as the RCTs (MD -2.32kg 95% CI -3.04 to -1.60).[62] however the longer duration retrospective cohort study led by Valensi et al found no significant reduction in weight: (MD -0.90kg 95% CI -2.26 to 0.46). (Figure 2.2B).[63]

Changes in body mass index were only reported in 2 studies and have been included in Appendix A for reference (Supplementary Figure 2A2).

2.4.6 Fasting Plasma Glucose (FPG)

Meta-analysis of the three RCTs showed that compared to sulphonylureas, treatment with sitagliptin produced similar change in fasting plasma glucose (mmol/l) from baseline (WMD 0.11 mmol/l 95% CI -0.08 to 0.29; I^2=0%)) (Figure 2.2C). Of the remaining RCTs, only the shorter 4.5 month RCT study led by Srivastava et al demonstrated a significant reduction in fasting plasma glucose; [MD 0.81mmol/l %; 95% confidence interval (CI) 0.70 to 0.92].[58]

The observational study led by Suraj et al also demonstrated a significant reduction in fasting plasma glucose with sulphonylureas compared to sitagliptin (MD 1.02 mmol/l; 95% CI 0.52 to 1.52).[62]

2.4.7 Blood Pressure and Lipid Changes

Two RCTs reported no significant difference between sitagliptin and sulphonylureas for change in systolic and diastolic blood pressure and level of triglycerides between study end and baseline (Figure 2.3 A-D).[53,55]

In the RCT led by Ahren et al, a statistically significant reduction in cholesterol from baseline was observed with sitagliptin compared to sulphonylureas (MD -0.16 mmol/mol 95% CI -0.29 to -0.03).[53]

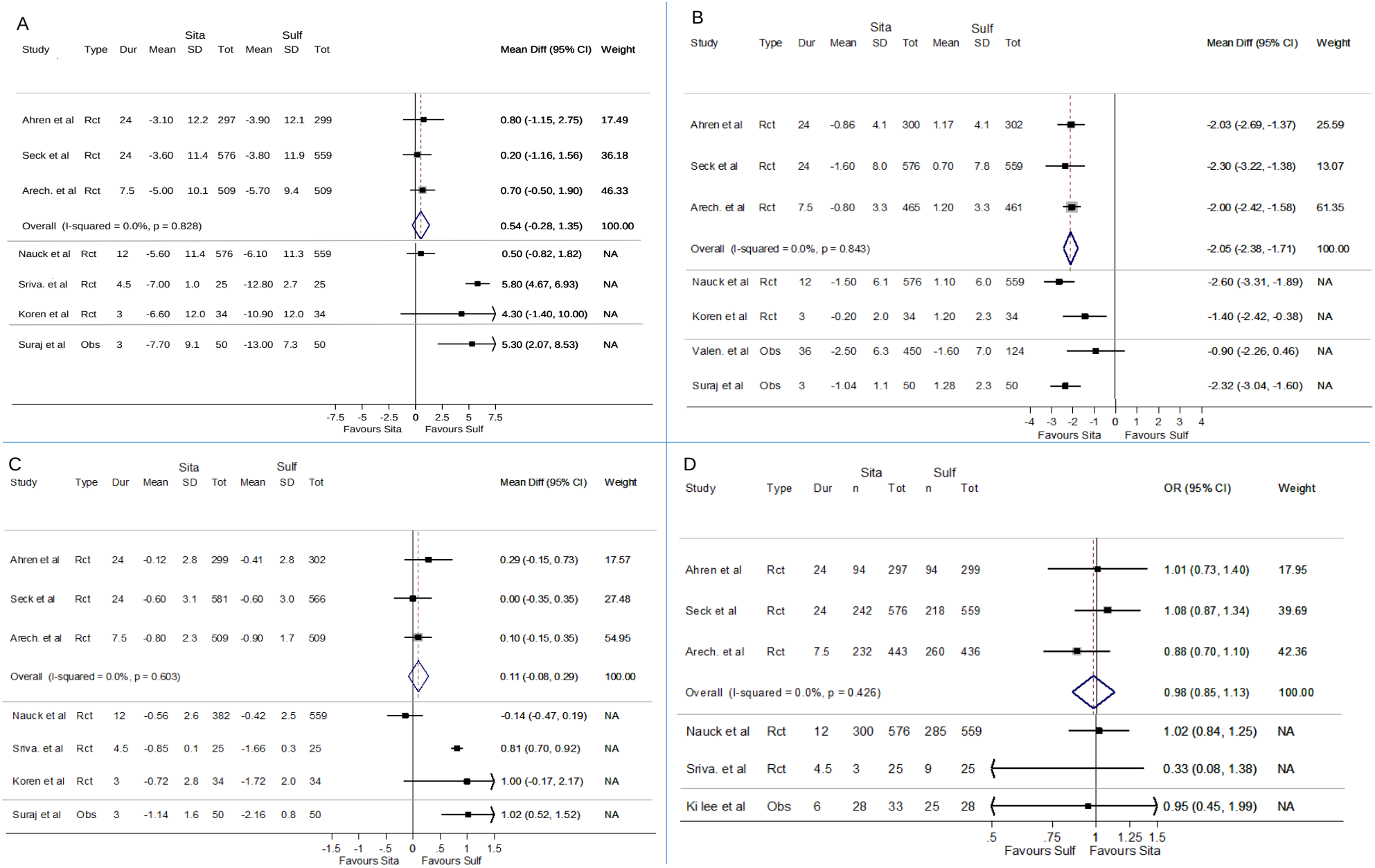


Figure 2.2 Forest plot comparing sitagliptin and sulphonylureas for change from baseline in HbA1c mmol/mol (A), weight, kg (B), fasting plasma glucose (mmol/l) (C) and proportions achieving a HbA1c< 53mmol/mol (< 7%) (D) at end of study. Rct=Randomized controlled trial, Obs=Observational study, Dur=duration in months, SD=Standard deviation, Tot=total participants, Mean Diff=mean difference, OR=Odds ratio, NA=not applicable, Sita=Sitagliptin, Sulf=sulphonylureas. Note: weights where present are from fixed effects meta-analysis though random-effects estimates were identical. Note: Figure taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 3).

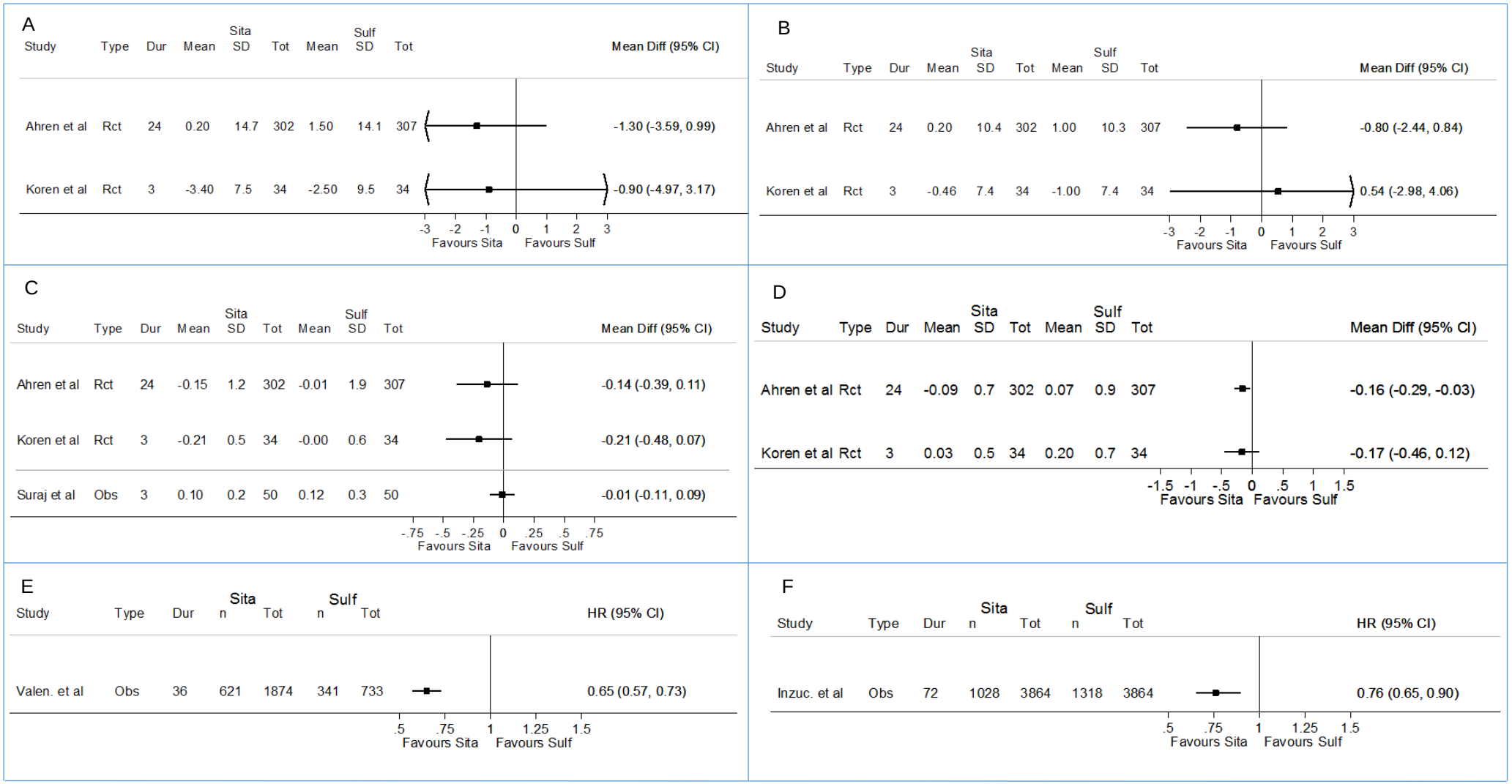


Figure 2.3 Forest plot comparing sitagliptin and sulphonylureas for change from baseline in systolic blood pressure mm Hg (A), diastolic blood pressure mm Hg (B), triglycerides, mmol/l (C), total cholesterol mmol/mol (D) and for risk of needing treatment change (E) and risk of initiating insulin (F);

Rct=Randomized controlled trial, Obs=Observational study, Dur=duration in months, SD=Standard deviation, Mean Diff=mean difference, HR=Hazard ratio, Sita=Sitagliptin, Sulf=sulphonylureas. Note: Figure taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 3).

2.4.8 Long-term Outcomes

Two observational studies led by Valensi et al and Inzucchi et al reported outcomes from longer follow-up of individuals not reported in any RCTs retrieved. The prospective cohort study led by Valensi et al compared the risk of needing treatment change after initiation with sitagliptin and sulphonylureas for a follow-up period of up to 36 months as shown in Figure 2.3E.[63] They found that the adjusted risk of needing treatment change was lower with sitagliptin; [Hazard Ratio (HR) 0.65 95% CI 0.57 to 0.73].

In the prospective cohort study led by Inzucchi et al, the risk of either group initiating on insulin treatment during a follow-up period of 72 months was calculated. They found that those prescribed sitagliptin had a lower risk of initiating insulin during follow-up, after relevant adjustment (HR 0.76 95% CI 0.65 to 0.90) (Figure 2.3F).[60]

2.5 Discussion

2.5.1 Summary of Results

In this systematic review, the meta-analysis conducted using three high quality randomized controlled trials (RCTs) in which follow-up was greater than 6 months,[40,53,57] demonstrated similar overall reduction in HbA1c and fasting plasma glucose after add-on of sitagliptin compared to sulphonylureas in individuals inadequately controlled on metformin. Statistically significant reduction in weight of approximately 2kg was observed with sitagliptin when compared to sulphonylureas driven by weight increase with sulphonylureas and decrease with sitagliptin. Outcome reporting for change in blood pressure and lipids from baseline was low and meta-analysis was not possible, though individual study results did not suggest any significant difference. Only one RCT led by Ahren et al showed a small statistical reduction in total cholesterol with sitagliptin compared to sulphonylureas, however it was too small in magnitude to be of clinical significance. Two cohort studies reported longer-term outcomes,[60,63] relating to time before a treatment change or insulin initiation was needed. In both of these high quality observational studies, results suggested that fewer individuals on sitagliptin than sulphonylureas needed treatment change at 36 and 72 months follow-up respectively.

I was unable to do a meta-analysis across all studies for any of the outcomes and only 3 studies were ultimately grouped for meta-analysis.[40,53,57] This was because of 3 reasons. Firstly, two studies (Nauck et al and Seck et al)[56,57] had overlapping patient populations; secondly, the

methodological approaches employed in the studies was different with both RCTs and observational studies included; and finally the duration of patient follow-up across studies was highly variable ranging from 1 to 72 months. However, appraisal of the studies revealed that the three high quality RCTs which exceeded 6 months in duration could be pooled together in a meta-analysis to retrieve more precise overall estimates.[40,53,57] Meta-analysis was undertaken with these 3 studies for change in HbA1c, weight, fasting plasma glucose from baseline and those achieving a HbA1c < 53mmol/mol and < 48 mmol/mol at the end of the study with no heterogeneity found for any of these estimates. When I undertook sensitivity analysis using random effects models for the meta-analysis, none of our estimates or confidence intervals changed.

Meta-analysis of high quality homogenous RCTs represents the highest source of evidence.[64] However, even though these 3 RCTs were homogenous, their inclusion criteria may have led to exclusion of important population subgroups frequently seen in clinical practice reducing the external validity of the findings. For example, Arechavaleta et al excluded individuals with a baseline HbA1c > 75 mmol/mol,[40] Seck et al excluded individuals > 78 years of age,[57] and Ahren et al excluded individuals with impaired renal function.[53] Drug utilization studies have shown that such criteria alone, may exclude close to 50% of individuals seen in "real world" clinical practice.[65] I also reported findings for other trials and observational studies which could not be meta-analysed to allow wider comparison, however populations in these studies (except for Valensi et al) [63] were no more representative of the "real world" as reflected in their inclusion and exclusion criterias.

2.5.2 Individual Outcomes in context

Glycaemic control achieved with sitagliptin or sulphonylureas in individuals inadequately controlled on metformin was similar in the meta-analysis of RCT studies examined in this review. One RCT led by Srivastava et al, and a prospective cohort study led by Suraj et al reported a more significant reduction in both HbA1c and fasting plasma glucose with sulphonylureas compared to sitagliptin, however these were both of 4.5 months in duration only.[58,62] This peak in sulphonylurea glycaemic efficacy within the first 6 months of treatment has been previously described.[66,67] However, for all studies of duration greater than 6 months, I found that glycaemic reduction with both sitagliptin or sulphonylureas was comparable. Guidance from ADA, NICE, IDF and EASD does not significantly discriminate between these two drugs for second-line usage after metformin to achieve glycaemic targets,[22,24,39,68] and my findings support this evidence.

Statistically significant weight loss with sitagliptin compared to sulphonylureas of approximately 2kg was evident in the meta-analysis and also across all RCTs and observational studies which had no more than 2 years of follow-up data. This difference was driven by weight decrease with sitagliptin and increase with sulphonylureas. Sitagliptin is often described as having only a weight neutral effect,[69-71] however, when compared directly with sulphonylureas, a reduction in weight is evident. A comparative reduction of this magnitude is of clinical significance and has been shown to improve physical and emotional health,[72] and is of most importance for individuals who are overweight or may be struggling to lose weight. This, in fact, can represent a significant proportion of individuals with T2DM.[9] The study led by Valensi et al with follow-up of 36 months found that weight reduction was evident, however it was not significant.[63] It is possible that by this stage (3 years after therapy initiation), the beneficial weight-loss effect of sitagliptin or conversely the negative weight-gain observed with sulphonylureas is somewhat negated.

Few studies reported data on impact of treatments on markers of cardiovascular health. Data reported in two RCTs,[53,55] did not provide evidence to suggest any clinically significant change being achieved in blood pressure or triglycerides through being prescribed sitagliptin or sulphonylureas after metformin. A small decrease was observed in cholesterol with sitagliptin in one RCT.[53] Such a reduction has been reported with other drugs in the gliptin therapeutic class and is not of any clinical significance.[73]

Longer-term outcomes among individuals followed up for greater than two years were reported in 2 cohort studies led by Valensi and Inzucchi et al respectively.[60,63] Both were deemed to be of high methodological quality.[60,63] The risk of either treatment group requiring a change in treatment or initiating insulin (in the latter study respectively) was lower with sitagliptin. The findings from both these studies suggest that individuals prescribed sitagliptin are less likely to need treatment change over longer durations of follow-up. However decisions to intensify treatment or initiate insulin therapy are based on clinician decisions, which can be subjective and hence will inevitably vary. Furthermore, treatment inertia is a well-established problem in care of individuals with T2DM.[74] Without data on glycaemic control at the time of treatment change, I could not fully assess whether the clinicians intensified treatment early, appropriately or late making this finding more challenging to interpret.

2.5.3 Strengths and Limitations of this study

This review undertaken has some important strengths. Firstly, this is the first systematic review, to my knowledge, to assess effectiveness from both RCTs and observational studies comparing

sitagliptin to sulphonylureas as add-on to metformin. Secondly, I have reported data across a wide range of outcomes beyond just glycaemic control and thirdly, I have undertaken meta-analysis only where deemed methodologically appropriate in accordance with a pre-specified protocol.[47]

There are also some limitations to acknowledge. Firstly, I have focused entirely on effectiveness in this review and not examined safety aspects. This was because they have been discussed in considerable depth elsewhere and are not central to this thesis whose focus is effectiveness. Secondly, my analysis has focused on sitagliptin only as it is the most widely used gliptin in the US and UK.[28] Sulphonylureas, however have been grouped together. Different sulphonylureas do exhibit different pharmacokinetic behavior, particularly with regards to their durations of action and newer agents have been attributed with potentially better safety profiles with respect to hypoglycaemic risks.[66] However, they do all act similarly from a pharmacological point of view.[66]

2.5.4 Gaps identified in the literature and implications for this thesis

This systematic review has identified several gaps in the literature where further research is needed. One gap identified in the literature was the absence of a cohort study in the UK evaluating effectiveness of sitagliptin compared to sulphonylureas in individuals inadequately controlled on metformin during routine clinical practice. This is needed as studies retrieved in this systematic review had inclusion and exclusion criterias which led to recruitment of individuals not entirely reflective of the "real world" in terms of baseline glycaemic control and comorbidity. Furthermore, there has been no exploration thus far of overall treatment effectiveness in term of achieving glycaemic targets as outlined by UK NICE guidance as well as how often a change in treatment is introduced when sitagliptin or a sulphonylureas are used after metformin in actual clinical practice. Studies thus far have not focused either on treatment effectiveness in older individuals such as those aged ≥75 years as evidenced by mean age range of 54.3 years to 59.6 years in the RCTs and 46.9 years to 64.2 years in the observational studies respectively for sitagliptin and sulphonylureas. This is a very important subgroup of individuals with T2DM who sometimes respond differently to pharmacotherapy than younger adults due to polypharmacy, comorbidity and altered pharmacokinetic handling of medications.[75]

Therefore, in this thesis, I will use "real world" data from UK primary care practices and my focus will be on examining the effectiveness of sitagliptin versus sulphonylureas across 4 outcomes: change in HbA1c from baseline, change in weight from baseline, examining the time before first recording of an elevated and undesirable HbA1c >58 mmol/mol and finally the time before a

treatment change is needed. I will first explore these outcomes in individuals aged ≥ 18 years and then investigate whether these finding differ in older individuals aged ≥75 years.

This systematic review has also highlighted gaps in the comparative effectiveness literature on sitagliptin and sulphonylureas with respect to longer-term microvascular and macrovascular complications of diabetes mellitus. These are outcomes that would be possible to explore in large observational clinical datasets with longer follow-up time. However at time of this PhD commencement, such large data was not available for sitagliptin. I will discuss future plans for addressing these longer-term outcomes in more detail in Chapter 11, the Discussion.

2.6 Context of this chapter in overall work

This systematic review of the literature has identified several gaps in comparative effectiveness literature relating to sitagliptin vs sulphonylureas in individuals inadequately controlled on metformin which are worthy of further investigation. Several of these outcomes will now form the basis and rationale behind the aims and objectives of this thesis as outlined in depth in Chapter 3. This chapter has also formed the basis of a published manuscript included in appendix for reference (Appendix H - Citation 3).

Chapter 3 Aims and Objectives

3.1 Overarching Aim and objectives

The overall aim of this thesis is to evaluate “real world” effectiveness of sitagliptin compared to sulphonylureas for individuals with type 2 diabetes mellitus (T2DM) as add-on to metformin.

More specifically, my objectives are to evaluate effectiveness of sitagliptin compared to sulphonylureas as add-on to metformin for the four outcomes below:

1) Glycaemic control as measured by comparative change in HbA1c from baseline after approximately 12 months

2) Weight control as measured by comparative change in weight from baseline after approximately 12 months

3) Time to first recording of an undesirable HbA1c > 58 mmol/mol

4) Time to first recording of an anti-diabetic treatment regimen change (prescribing of an alternate anti-diabetic treatment)

I will examine these outcomes by undertaking cohort studies using “real world” data from primary care practices based throughout the UK.

3.2 Justification for this Thesis

Sitagliptin is one commonly used treatment option for the management of T2DM. It emerged in 2007 as the first licensed in its pharmacological class of dipeptidy-peptidase-4 inhibitor (DPP-4) (more commonly referred to as gliptins) and became the most widely used gliptin in both the UK and US.[28] Alongside metformin, sulphonylureas are the most widely prescribed oral anti-diabetic agent for T2DM.[76] I have described in my systematic review in Chapter 2, that one of the most challenging prescribing decisions in T2DM involves choosing between sitagliptin or sulphonylureas when first-line therapy with metformin alone has proved inadequate. In my review, I highlighted that safety of these treatments has been evaluated in considerable depth, however further work is needed to help clinicians become more informed on their comparative effectiveness. The systematic review showed that there was no difference between sitagliptin and sulphonylureas in terms of HbA1c change across randomised controlled trials and some cohort studies. Though randomised controlled trials are indeed the gold standard in evaluating effectiveness, they are costly to run, time-consuming to organise and sometimes not feasible for particular population subgroups. For example, across all trials included in the systematic review, it was notable that more comorbid individuals and older individuals especially those aged ≥ 75

years were excluded. Furthermore, it is sometime found that treatments exhibit different effectiveness when they start being used in “real world” practice compared to that demonstrated in trials due to worse adherence rates, lower thresholds for tolerability of adverse effects, and often less intensive monitoring. This is why data collected during routine clinical practice can have a very important role in giving insight into “real world” effectiveness. This thesis will use such routinely collected, “real world” data from primary care practices to evaluate effectiveness of sitagliptin compared to sulphonylureas as add-on to metformin with a particular focus on those aged ≥ 75 years.

My systematic review highlighted several further areas where further comparative effectiveness work is needed. There has been no exploration thus far of overall treatment effectiveness in terms of achieving actual glycaemic targets as outlined by guidance from the National Institute for Health and Care Excellence (NICE),[22] as well as how often a change in anti-diabetic treatment is needed and introduced when sitagliptin or a sulphonylureas are used after metformin. These areas will also become a focus for investigation in this thesis.

3.3 Structure of the Thesis

3.3.1 Brief Overview

The remaining chapters in this thesis have been structured to allow me to achieve the objectives outlined above in Section 3.1. I will do this as follows.

In Chapter 4, I will introduce The Health Improvement Network (THIN), primary care database. This is the database containing the UK primary care electronic health care records which I will be using to undertake my cohort studies. I will use THIN to create a cohort of individuals with T2DM. In Chapter 5, I will evaluate this cohort, and explore how the diagnosis of T2DM has changed over time, comparing my findings to current literature and more crucially examine prescribing patterns of anti-diabetic medication between 2000 and 2013. This will enable me to get a better understanding of how I can extract individuals prescribed sitagliptin and sulphonylureas as add-on to metformin and provide insight into the design of the cohort studies to complete the objectives listed above in Section 3.1.

In Chapter 6, I will explore the demographic and clinical characteristics of the cohort of individuals initiated on sitagliptin and sulphonylureas as add-on to metformin. I will determine which factors most influence clinicians to prescribe sitagliptin or sulphonylureas as add-on to metformin. In Chapter 7, I will then explore recording of the four outcomes of interest: HbA1c, weight, HbA1c >

58 mmol/mol and treatment change respectively. This will help me determine the factors that influence the recording of these outcomes and how well they are recorded.

In Chapter 8, I will introduce some methodological concepts - relating to the use of propensity score matching and causal diagrams which will be subsequently used in the cohort studies in Chapters 9 and 10.

I will present the cohort studies examining change in HbA1c and weight from baseline in both individuals aged ≥18 years and older individuals aged ≥75 specifically in Chapter 9. In Chapter 10, I will present the cohort studies examining the time to first recording of a HbA1c > 58 mmol/mol and first recording of a treatment change. I will explore this for both adults aged ≥18 and older adults aged ≥75 years. In Chapter 11, I will present a discussion of findings from this thesis and place them in the context of existing knowledge, highlighting the strengths and limitations of this thesis and outlining the main implications of this work for clinical practice, public health and future research.

Below, I more specifically outline the contents of each remaining chapter:

3.3.2 Specific Chapter Outline

The content of each chapter is detailed below:

Chapter 4 – The Data Source and the Diabetes Cohort

1. Rationale for using The Health Improvement Network (THIN) primary care database in this thesis.
2. Key strengths and limitations of THIN
3. Algorithms developed and used to identify a cohort of individuals with T2DM mellitus using THIN
4. Strengths and limitations of the algorithms devised

Chapter 5 – Trends in recording of diagnosis and prescribing in type 2 diabetes mellitus

1. Annual changes in the incidence of recording of diagnoses for T2DM
2. Annual changes in the prevalence of diagnoses for T2DM
3. Annual changes in prescribing of anti-diabetic agents among individuals diagnosed with T2DM particularly for first line use and as second line add-on therapy
4. Strengths and limitations of the study presented

Chapter 6 - Investigating patterns of prescribing for sitagliptin and sulphonylureas as add-on to metformin

1. Similarities and differences among individuals prescribed sitagliptin or sulphonylureas as add-on to metformin in terms of demographic characteristics, comorbidities and concomitantly prescribed treatments.
2. Important demographic and clinical characteristics associated with prescribers' decisions to commence sitagliptin as opposed to sulphonylureas.

Chapter 7 - Investigating recording of the outcomes

A comparison across those initiated on sitagliptin vs sulphonylureas as add-on to metformin for:

1. Length of follow-up time available for individuals following the index date
2. Frequency of recording of HbA1c over time
3. Frequency of recording of weight over time

An analysis of those initiated on either sitagliptin or sulphonylureas as add-on to metformin for

4. Frequency of recording of first HbA1c > 58 mmol/mol over time
5. Frequency of recording of first change in anti-diabetic treatment (through prescribing of an anti-diabetic other than metformin and sitagliptin or sulphonylureas respectively) over time

Additionally, I will explore the

6. Relationship between (i) change in HbA1c from baseline, (ii) change in weight from baseline, (iii) recording of first HbA1c > 58 mmol/mol and (iv) recording of first change in anti-diabetic treatment with covariates related to demographics, comorbidities and prescribed medications among those initiated on either sitagliptin or sulphonylureas as add-on to metformin
7. Identify those characteristics that most influence (i) change in HbA1c, (ii) change in weight, (iii) recording of first HbA1c > 58 mmol/mol and (iv) recording of first change in anti-diabetic treatment among those initiated on either sitagliptin or sulphonylureas as add-on to metformin

Chapter 8 Alternative approaches to handling the challenge of confounding in observational studies

1. Use of causal diagrams, specifically direct acyclic graphs (DAGs) in epidemiological studies
2. Use of Propensity score matching methods in epidemiological studies

Chapter 9 Cohort studies examining change in HbA1c and weight from baseline

1. Change in HbA1c approximately 12 months from baseline in individuals aged ≥ 18 years prescribed sitagliptin compared to sulphonylureas as add-on to metformin
2. Investigation of how changes observed in 1) differ in individuals aged ≥ 75 years compared to those aged 18-75 years
3. Change in weight approximately 12 months from baseline among individuals aged ≥ 18 years prescribed sitagliptin compared to sulphonylureas as add-on to metformin
4. Investigation of how changes observed in 3) differ in individuals aged ≥ 75 years compared to those aged 18-75 years

Chapter 10 Cohort studies examining first recording of a HbA1c > 58 mmol/mol and first recording of a treatment regimen change

1. Examination of time to first recording of a HbA1c > 58 mmol/mol among individuals aged ≥ 18 prescribed sitagliptin or sulphonylureas as add-on to metformin.
2. Examination of how rates of first recording of a HbA1c > 58 mmol/mol observed in 1) differ in individuals aged ≥ 75 years compared to those aged 18-75 years
3. Examination of time to first anti-diabetic treatment regimen change among individuals aged ≥ 18 prescribed sitagliptin or sulphonylureas as add-on to metformin.
4. Examination of how rates of first recording of an anti-diabetic treatment change observed in 3) differs in individuals aged ≥ 75 years compared to those aged 18-75 years
5. Descriptive assessment of clinician response to recording of a HbA1c > 58 mmol/mol for an individual by determining if an anti-diabetic treatment change was introduced, doses were changed or no action was taken.

Chapter 11 Discussion

1. Summary of the main findings of this thesis.
2. Placing the findings of this thesis within the context of existing literature
3. Strengths and limitations of the work completed in this thesis
4. Implications of the findings in this thesis for clinical practice, public health and future research.

3.4 Context of this chapter in overall work

The purpose of this chapter was to outline in detail the overall aim and objectives of this thesis and provide a summary of the justification behind this research project. I have also provided an overview of the specific contents for each of the remaining chapters in this thesis.

Chapter 4 The Data Source and the Diabetes Cohort

4.1 Chapter Overview

In this chapter, I will justify my use of an observational study design to evaluate effectiveness of treatments for type 2 diabetes mellitus (T2DM), using The Health Improvement Network (THIN). I will then describe the THIN database and highlight its strengths and limitations. In the latter half of this chapter, I will describe the algorithm used to extract the cohort of individuals with T2DM from the THIN database.

4.2 Why use an observational study design to examine treatment effectiveness?

The randomised study design is the gold standard for examining efficacy of an intervention as it ensures that treatment allocation can be undertaken independently of baseline characteristics.[77] This ensures both known and unknown confounders are controlled for in the analysis. The challenge of randomised study designs, however, are the costs, recruitment challenges as well as the additional regulatory monitoring over and above that done clinically.[77] Furthermore, the restrictions imposed on a randomised study by its often strict inclusion and exclusion criteria means that they include only a subset of the study population of interest. Thus, they may not necessarily reflect the population encountered in "real world" clinical practice.[77] Thus, it is sometimes found that when the trial findings are applied to a "real world" setting, the intervention may actually exhibit a different degree of effectiveness.

Observational studies using routinely collected data for clinical care offer an attractive alternative to randomised studies, and if designed correctly, they are more representative of actual clinical practice, less costly and can often facilitate analysis on a much larger scale and in individual subgroups that otherwise could not examined. They reflect clinical decisions and outcomes from real-time patient care rather than an often "idealised" randomised study scenario.[78] However, this also means treatment is not randomised and in fact, can be biased by the prescriber's view on how they perceive the treatment may influence future beneficial and adverse health outcomes.[79] This lack of randomisation means that a simple direct comparison of treated and untreated individuals for example, may lead one to erroneously conclude that treatment is harmful when in fact, it may be given to those at greater risk of harm.[79] The approach to preventing such erroneous conclusions involves first carefully identifying those variables that may affect both choice of

treatment and the occurrence of the outcome, otherwise known as confounding variables. Secondly, once identified, these confounders must be accounted for in the statistical approaches used to complete the analysis. Identifying these confounders is not always straightforward, however, and there are different approaches that can be used. In Chapters 6 and 7, I will explore which covariates are associated with both my exposure (prescribing of sitagliptin or sulphonylureas) and each outcome of interest to help identify the potential confounders. In Chapter 8, I will present an alternate approach to identify confounders which is underpinned by theoretical understanding of the clinical questions and makes use of causal diagrams.[80] Regardless of the approach adopted to identify confounders, the strengths and limitations of the data available must also be taken into account, as not all variables may be sufficiently well reported.[81]

Although, I have highlighted the reasons why an observational study can be useful in evaluating treatment effectiveness, I have also presented several challenges which must be considered in the study design. Further information on methodological approaches to handling confounding and undertaking observational studies will be presented in Chapter 8.

4.3 Data Source

4.3.1 Why use The Health Improvement Network (THIN)?

Several databases are available in the UK that provide access to routinely collected healthcare data. Some are secondary care databases such as Hospital Episode Statistics while primary care databases available include the Clinical Practice Research Datalink (CPRD), QResearch and THIN. My first decision was to use a primary care database because it is well established that individuals with diabetes mellitus (DM) in the UK are managed largely in primary care,[82] rather than through specialised services alone. This means that most cases particularly in the earlier stages of disease treatment where I intend to focus, would be managed largely in primary care.

The second decision concerned choosing one particular database to use among the primary care database options. In terms of size, data coverage, and quality, studies have shown all three to be relatively similar and indeed have significant overlap.[83,84] THIN was selected as both my supervisors and I were experienced with its usage and a full license from IMS Health to access the THIN database was available within the department.

4.3.2 Summary of THIN

The Health Improvement Network (THIN) is one of the largest primary care databases collecting anonymised information on individual demographic, disease diagnosis, management and prescribing from UK primary care. In 2013, THIN was reported to contain medical records from around 587 general practices throughout the UK with around 12 million individuals contributing data.[85] It has been shown to be broadly representative of the UK population.[86,87] Information stored in THIN is collected during routine patient consultations with General Practitioners and other staff from when an individual registers at a general practice affiliated with THIN to when they leave the practice or die. Data in THIN is stored across several sets of files created for each practice. This includes patient record files detailing demographic data, postcode variable indicator files detailed measures of deprivation in the form of quintiles of Townsend score and medical record files contain diagnoses and symptoms recorded during consultations. Therapy records containing prescription data and additional health records with information on immunizations and test results e.g. weight, height, HbA1c, creatinine etc. are also included. Patient records across all of these files are linked via a patient identifier called the "patid" as shown in Figure 4.1. Symptoms, diagnoses and disease monitoring are recorded using the Read codes, hierarchical coding system.[88,89] Prescription data recorded within therapy records detail the medication type, brand, dosage, quantity and date of prescription issue. Each medication type and strength is also assigned a unique identifier known as a drugcode. THIN also provides information on patient referrals made, secondary care discharge letters and anonymised free text information.[90] Some free text information is made available in THIN as part of the database and comprises of information retrieved using searches that have been previously requested for specific studies. However in many instances if free text searches are required, IMS health who provide access to THIN, must be contacted and there will be additional payment required.

THIN is updated annually. For this thesis, all projects will be undertaken using THIN Version 1501. This was the most recent version available at time of commencement of this work and included data at a minimum to the end of 2014 from each practice.

4.3.3 Codelist generation

Using Read code dictionaries, lists can be created to identify individuals with different symptoms and disease such as diabetes mellitus (DM).[89] Lists of drugcodes can be created to help identify individuals prescribed relevant medications of interest. Finally, clinical monitoring and measurements e.g. HbA1c test results, weight etc. recorded within the additional health record

files can be accessed using the dictionary for AHD codes. Examples of codelists such as the diabetes codelists developed and employed in later studies are included in Appendix B (Supplementary Tables 4A1-4A4).

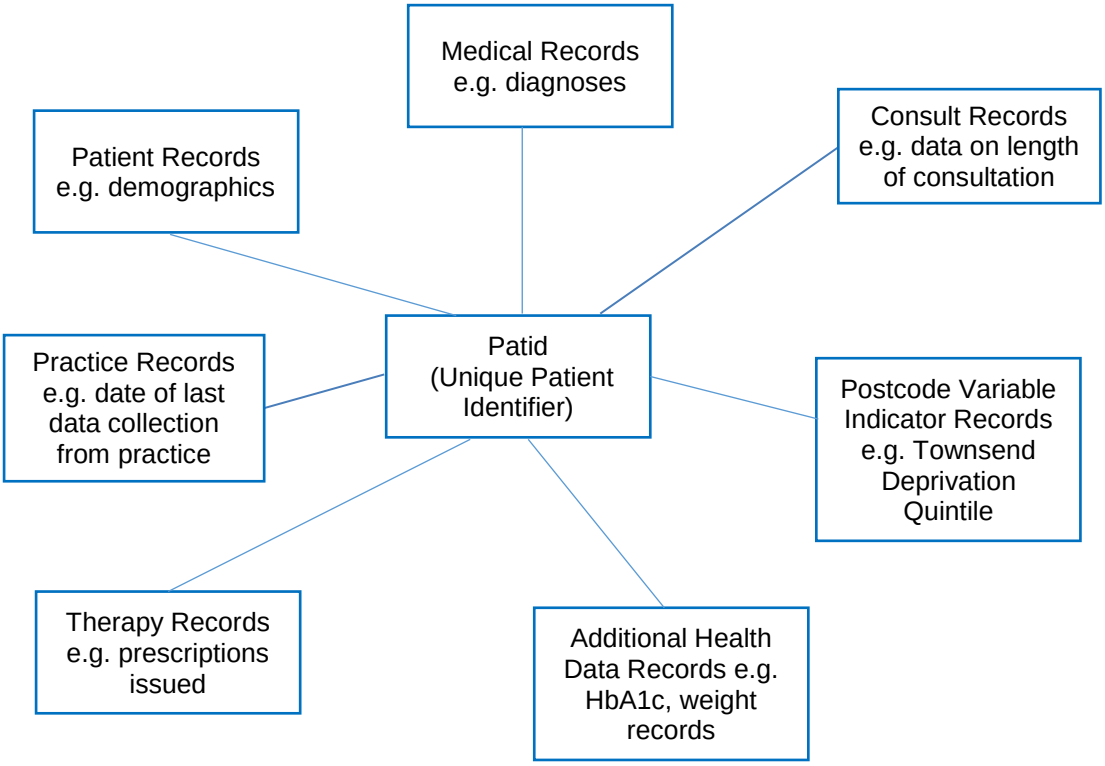


Figure 4.1 Linkage of records in THIN via patient identifier (patid)

4.3.4 Measures of data quality in THIN

There are several markers of data quality embedded within THIN such as the generation of variables such as “patflag” and “therflag” which categorise records based on their integrity according to internally validated algorithms inbuilt in THIN. There are also additional measures of quality assurance for THIN data that I have included to ensure high level of data quality. The acceptable mortality reporting (AMR) and acceptable computer usage (ACU) standards in THIN are two such dates that have been created in THIN through use of algorithms.[91,92]. The AMR date is the date after which the practice is confirmed to have a rate of mortality sufficiently similar to that expected for a practice with its demographic characteristics, based on data from the Office for National Statistics.[91] This was introduced as a measure of quality in 1990s, because as practices transitioned from paper to electronic based medical records they only transferred across live patients which could distort mortality rates. For a similar reason, I also include the ACU date which is the date after which a practice is likely to use their computer system fully for recording.

This was defined as practices which on average have at least one medical record, one additional health record and two prescriptions per individual per year.[92]

4.3.5 Strengths and limitations of THIN

There are several benefits of using THIN for clinical research related to DM as is proposed in this thesis. The large size of the database provides a means of getting access to "real world" patient data which is representative of the UK and conduct studies of a size that may not be economically viable using a randomized controlled trial.[85] The data contained within THIN is longitudinal and comprehensive in nature with respect to diagnoses, referrals, prescribing and monitoring. This is key as individuals with T2DM are known to be managed largely in primary care.[82] Furthermore, as the monitoring of individuals with DM has been financially incentivised as part of the quality and outcome framework since 2004, primary care data quality has further improved for individuals with DM since 2004.[93]

There are however several limitations when using THIN for such work. Secondary care data, particularly acute prescribing, is absent from the database. All significant secondary care diagnoses should in theory be retrospectively entered into the individuals' primary care records though studies have shown that this is not always the case.[94] The large size of the database often means that statistical analysis identifies even minor changes as significant and therefore careful interpretation is required to distinguish statistical and clinical significance. The data is entered by staff during routine patient consultations in primary care, and is not entered for research purposes. Though this is advantageous in that data is more reflective of actual clinical practice, it also means that endpoints or other outcomes being investigated may not necessarily be recorded at the exact time points our research question may require them. Finally, a prescribing record for a drug in THIN does not equate necessarily to adherence to therapy. Though surrogate measures of adherence can be applied in THIN, for example, by examining time between the issue of successive prescriptions. This cannot guarantee an individual is taking the medication as prescribed. This challenge of adherence is however, not exclusive to work with THIN or indeed observational data and is a major challenge in all forms of pharmacoepidemiological and clinical trials research. Some clinical trials even adopt pill counting to measure adherence which in itself can be inappropriate as it makes results less reflective of the "real world".[95]

Thus, THIN remain a very useful resource for "real world" health research provided researchers are aware of the limitations detailed above and ensure that any study is designed to minimise

their impact. This usefulness of THIN has been exemplified in several pieces of important work completed in the discipline of DM in recent years.[96,97]

4.3.6 Covariate Definitions

There are several variables I will refer to later in this thesis when I present the cohort studies. Some of these variables are embedded within THIN while others will be created. These variables are described below:

General:

Date of T2DM diagnosis: Date on which a diagnosis of T2DM was first recorded

Year of T2DM diagnosis: Year in which T2DM was diagnosed

Age of T2DM diagnosis: Calculated from date of first record of T2DM - date of birth

Index date: This will be introduced as a covariate in Chapter 6 and refers to the date on which the first prescription for either sitagliptin or sulphonylureas was issued. Baseline covariate data will be collected on or before this date unless otherwise specified below.

Year of entry: Year in which first prescription for either sitagliptin or sulphonylureas was issued.

Age at entry: Calculated using date of entry minus the date of birth recorded in THIN (date of birth in THIN is not recorded precisely in order to ensure anonymization of data and is usually rounded to beginning, middle or end of month)

Face to Face Consultation frequency (F2FC): This was calculated by determining the average number of face to face consultations (as identified from consultation records) per individual per year over the course of their registration with the THIN affiliated GP practice.

Sex: Held in THIN patient record

Smoking Status: I classified smoking status as: current smoker, ex-smoker and never smoker. This categorical variable was generated based on an algorithm which identified Read Codes in the medical and additional health records indicating smoking status. I also identified individuals on smoking cessation therapy. These were classified as current smoker as they were assumed to only very recently have given up cigarettes and given the high rates of failure on smoking cessation treatments. Smoking status was ascertained based on record entered closest to index date.

Townsend Quintile: This is a measure of social deprivation and in THIN divided into 5 quintiles with the 5th (lowest quintile) referring to the most deprived and 1st being the least deprived.[98,99] The Townsend quintiles were derived on the basis of the 2001 census data and linked to

households via postcodes by the data providers. They are calculated based on socioeconomic, ethnic and environmental indices.

Ethnicity: This variable is known to be inconsistently captured in UK primary care.[100] I will use 5 ethnic domains to capture this based on Read codes recorded for individuals: White, Asian, Black, Mixed and Unknown.

History of hypoglycaemias: Individuals with either a Read code indicative of hypoglycaemia or freetext entry recorded in THIN indicative of hypoglycaemic history.

History of excessive alcohol intake: This history will be determined through use of Read codes as well as additional health records that provide data on alcohol units consumed per week. The threshold applied to determine a history of excessive alcohol use was ≥ 28 units for women and ≥ 35 units per week for men. These thresholds bring consumption into the range that would be described as "hazardous drinking" by the Institute of Alcohol Studies and most national guidelines.[101]

Variables measured at baseline

Baseline HbA1c (mmol/mol): Latest HbA1c recorded from 6 months prior to index date to no later than 14 days after the index date.

Baseline weight (kg): Latest weight recorded from within 12 months prior to index date to no later than 14 days after the index date.

Baseline Body Mass Index (BMI) kg/m^2: Latest BMI recorded from within 12 months prior to index date to no later than 14 days after the index date.

Baseline Systolic and Diastolic Blood Pressure: Latest blood pressure recorded within 12 months prior to index date.

Baseline Total Cholesterol (mmol/L): Latest **t**otal cholesterol recorded within 12 months prior to index date.

Fasting Plasma Glucose (mmol/l): Latest fasting plasma glucose reading recorded within 12 months prior to index date.

Metformin dose (<1500mg or >1500mg): Binary variable to indicate dose of metformin calculated from dosage instructions and tablet strength recorded in THIN therapy records

Sulphonylurea type: The type of sulphonylureas prescribed at the index date will be recorded as gliclazide, glipizide, tolbutamide, chlorpropamide, glimepiride and other.

Comorbidities

Individuals were classified as having any of the comorbidities below if they had a Read code in their medical record belonging to disease code lists that were prepared for each disease and then independently reviewed by a clinician.[89] These codelists are available upon request and have not been included in the appendix due to their significant volume:

Cancer, Cardiovascular disease, Heart Failure (HF Read code or on anti-HF med), Chronic Kidney Disease, Liver disease, Hyperthyroidism, Hypothyroidism, Anaemias

Cardiac Arrythmia, Dementia, Epilepsy

Medication

Individuals prescribed any of the following classes of medications were identified through code lists prepared for each medications with use of the British National Formulary (BNF) and the THIN 15 drug dictionary.[89] Detailed drug codelists for anti-diabetic medication are available in Appendix B (all other medication codelists are available upon request). Individuals were described as being on a prescribed medication if they received a prescription for any of the medication classes below within the 3 months prior to the index date.

Anti-hypertensive, Anti-anginals, Diuretics, Antiplatelet, Anticoagulant, Antiobesity, Statins, Other lipid lowering drugs, thyroxine, Anti-thyroid drugs, Antidepressants, Antipsychotics, Steroids (Oral/Intravenous), Anticonvulsants

4.4 Generating the Diabetes Mellitus Cohort

4.4.1 Overview

In order to examine the effectiveness of sitagliptin compared to sulphonylureas as add-on to metformin, I initially had to identify individuals with T2DM. This was done in THIN by developing a two-step algorithm in collaboration with a second researcher, Sonia Coton who was also involved with each step of development, validation and implementation of this algorithm. The first step was to identify individuals with diabetes mellitus (DM) and the second step was to classify them into T2DM, type 1 diabetes mellitus (T1DM) or other types of DM. Both algorithms were developed through consultation with a multidisciplinary clinical research team as detailed below.

4.4.2 Cohort Description

Only data that met quality assurance criteria in THIN as determined by the acceptable mortality reporting and acceptable computer usage standards described earlier (Section 4.3.4) was used.[91,92] All individuals aged 0–99 years who were registered with a general practice contributing

data between 1 January 2000 and 31 December 2014 and had at least one year of quality assured data following registration were included. Scientific approval to undertake this study was obtained from CMD Medical Research's Scientific Review Committee in February 2015. (SRC Reference Number: 15-011).

4.4.3 Algorithm generation

4.4.3.1 Algorithm 1 - Identification of individuals with potential type 1 and type 2 diabetes mellitus

A list of Read codes, drugcodes and AHD codes indicative of DM was prepared (included in Appendix B - Supplementary Tables 4A1-4A4), in consultation with a clinician (Prof Irwin Nazareth). All individuals with any such code indicative of DM in their healthcare record were then identified. I then removed individuals that had no DM records except for metformin prescriptions (potential polycystic ovary syndrome cases), individuals with only a single record of DM and individuals which had no diagnostic record (Read code or AHD code) for DM.

Sensitivity analysis on individuals remaining revealed that one particular AHD code being used entitled "HbA1c diabetic control" was misclassifying cases as DM. Though this code was designed for use in monitoring of DM individuals, exploration revealed that general practitioners (GPs) were also using this code among non-diabetic and pre-diabetic individuals as well (potentially for screening purposes). To overcome this problem, individuals who had been assigned as having DM due only to the presence of this code were examined. If they had a HbA1c result above the World Health Organisation recommended threshold value of 48 mmol/mol (6.5%) these individuals were classified as having DM otherwise they were excluded.[15]

Finally individuals with diagnostic codes for other DM subtypes only were excluded e.g. gestational diabetes. The first record of any of the following was considered the date of diagnosis for DM; (1) a diagnostic code for diabetes (2) supporting evidence of diabetes e.g. screening for diabetic retinopathy or (3) treatment for diabetes.

4.4.3.2 Algorithm 2 - Classification of individuals with DM as type 1 or type 2

Within the cohort of individuals identified with potential T1DM or T2DM above, I generated the five variables below to help distinguish DM type. These are listed below in descending level of importance:

- Diagnostic code type assigned
- Cumulative days of other anti-diabetic (non-insulin) prescriptions
- Number of insulin prescriptions

- Incident or prevalent case
- Age of first record of DM

Diagnostic code type assigned

I categorized individuals into 4 groups: those with only T1DM-specific diagnostic codes used in their healthcare record, those with only T2DM-specific codes used in their healthcare record, those with T1DM-specific and T2DM-specific codes used in their record (possibly due to diagnostic or coding errors) and finally those with only non-specific DM diagnostic codes only. Examples of Read codes used are detailed in Table 4.1 below and in full in Appendix B (Supplementary Tables 4A1-4A4).

Table 4.1 Example of diabetes mellitus Read codes

Read Code	Description	Code-type
C10E611	type i diabetes mellitus with gangrene	T1DM
C108011	type i diabetes mellitus with renal complications	T1DM
C108411	unstable type i diabetes mellitus	T1DM
C10EA00	type 1 diabetes mellitus without complication	T1DM
C109D11	type ii diabetes mellitus with hypoglycaemic coma	T2DM
C10F700	type 2 diabetes mellitus - poor control	T2DM
C10FJ11	insulin treated type ii diabetes mellitus	T2DM
C10F000	type 2 diabetes mellitus with renal complications	T2DM
C107y00	other specified diabetes mellitus with periph circ co	Non-Specific
2G5I.00	o/e - left diabetic foot at low risk	Non-Specific
ZC2C800	dietary advice for diabetes mellitus	Non-Specific
F372.11	diabetic polyneuropathy	Non-Specific

T1DM=type 1 diabetes mellitus, T2DM=type 2 diabetes mellitus, o/e=on examination, periph circ co=peripheral circulation complications
Note: Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 2).

Cumulative days of other anti-diabetic prescriptions

The number of days an individual was prescribed other anti-diabetic (non-insulin) treatment was determined by dividing the quantity of medication issued by the daily dose the individuals were on. For instances where either of these variables were missing, I used a deterministic method of imputing quantity or daily dose based on examining what was common for that medication

quantity or daily dose in individuals where values were recorded e.g. issue of 28 sitagliptin 100mg tablets would most commonly relate to a dose of one tablet daily, hence the prescription was judged to be a 28 day prescription. Where information was completely missing for quantity and daily dose, I assumed prescription was for 28 days as exploratory analysis revealed that the majority of DM treatments in THIN were issued for this duration.

The number of insulin prescriptions issued

The total number of insulin prescriptions issued per individual was also determined. The duration of insulin prescription was not determined due to the fact that dosage information was not commonly recorded for insulins.[9]

Incident or prevalent case

Mamtani and colleagues completed extensive work which showed that if the first record of DM appeared 9 or more months after registering with a general practice, individuals were more likely to be incident cases of DM.[16] However, if the first record of DM appeared within 9 months after registration, this is most likely due to the recording of a DM diagnosis for individuals who already had the disease when they registered at that practice.[16] This application allowed me to identify likely incident and prevalent cases. This was useful as it allowed me to ascertain whether I had a complete DM record for an individual or whether there was potentially historical DM data for an individual from before practice registration, I may not have access to.

Age of diagnosis of DM

Age of diagnosis of DM was calculated for individuals who were classified as incident cases (first record of DM appearing more than 9 months after practice registration) and for those individuals who had a record of DM that pre-dated their practice registration (entered retrospectively into their healthcare record after practice registration). The first date for a record of DM when pre-registration records were included helped inform when the disease was first diagnosed for that individual. There was a subset of individuals whose first record of DM appeared between 0 and 9 months after practice registration for whom the age of diagnosis could not be confirmed. I used, when necessary, guidance from the Royal College of General Physicians that recommends the age threshold of 35 years for distinguishing between T1DM and T2DM.[9]

4.4.3.3 Validation

In order to internally validate this classification algorithm, the full electronic healthcare records of a practically feasible sample of 500 individuals identified with DM was chosen at random from THIN. This sample included both cases classified by the algorithm as T1DM and T2DM. The

record was then examined and classified into diabetes type separately based on assessment of the entire individuals medical, prescription and additional health records available. This assessment served as my reference standard. The classification assigned to these 500 individuals by manual record assessment was then compared to my classification by algorithmic methods to ascertain diagnostic accuracy of the algorithm.

4.4.4 Application of the Algorithm

4.4.4.1 Algorithm 1 - Identification of individuals with potential type 1 and type 2 DM

In total, 9,161,866 individuals aged 0-99 years between 2000-2014 were identified. From this cohort, 457,918 individuals with potential T1DM or T2DM were identified. The number of individuals removed at each step during the application of the algorithm is illustrated in Figure 4.2.

4.4.4.2 Algorithm 2 - Classification of individuals with DM as type 1 or type 2

Of the cohort of 457,918 identified through use of algorithm 1, 37,693 (8.2%) individuals were classified as having T1DM, 418,433 (91.4%) as T2DM and 1,792 (0.4%) individuals remained unclassified (Figure 4.3). Only 1,155 (3.1%) of all individuals with T1DM and 6,139 (1.5%) of all individuals with T2DM were classified with some degree of uncertainty. Thus, the vast majority of individuals were classified with confidence (36,538 (96.9%) of all individuals with T1DM and 412,294 (98.5%) of all individuals with T2DM).

The full criteria for classification of individuals into T1DM and T2DM is detailed in Table 4.2 and summarized below in Figure 4.3. Unspecific diagnostic codes refers to when both a T1DM code and T2DM code was used in the same individual record or when no type-specific code was used to record an individual's DM diagnosis. The individuals classified with uncertainty are highlighted with an asterisk below and in Table 4.2.

Individuals with type 1 diabetes mellitus met one of the following criteria:

1. A diagnostic code of T1DM only and prescription for insulin only.
2. A diagnostic code of T1DM only, a prescription for insulin and less than 6 months cumulatively of other anti-diabetic agents.
3. T2DM code only or unspecific diagnostic codes, a prescription for insulin only and were an incident case of DM or diagnosed with DM under the age of 35.
4. Unspecific diagnostic codes, a prescription for insulin, less than 6 months cumulatively of other anti-diabetic agents and were an incident case of DM or diagnosed with DM under the age of 35.*

*Individuals classified with uncertainty

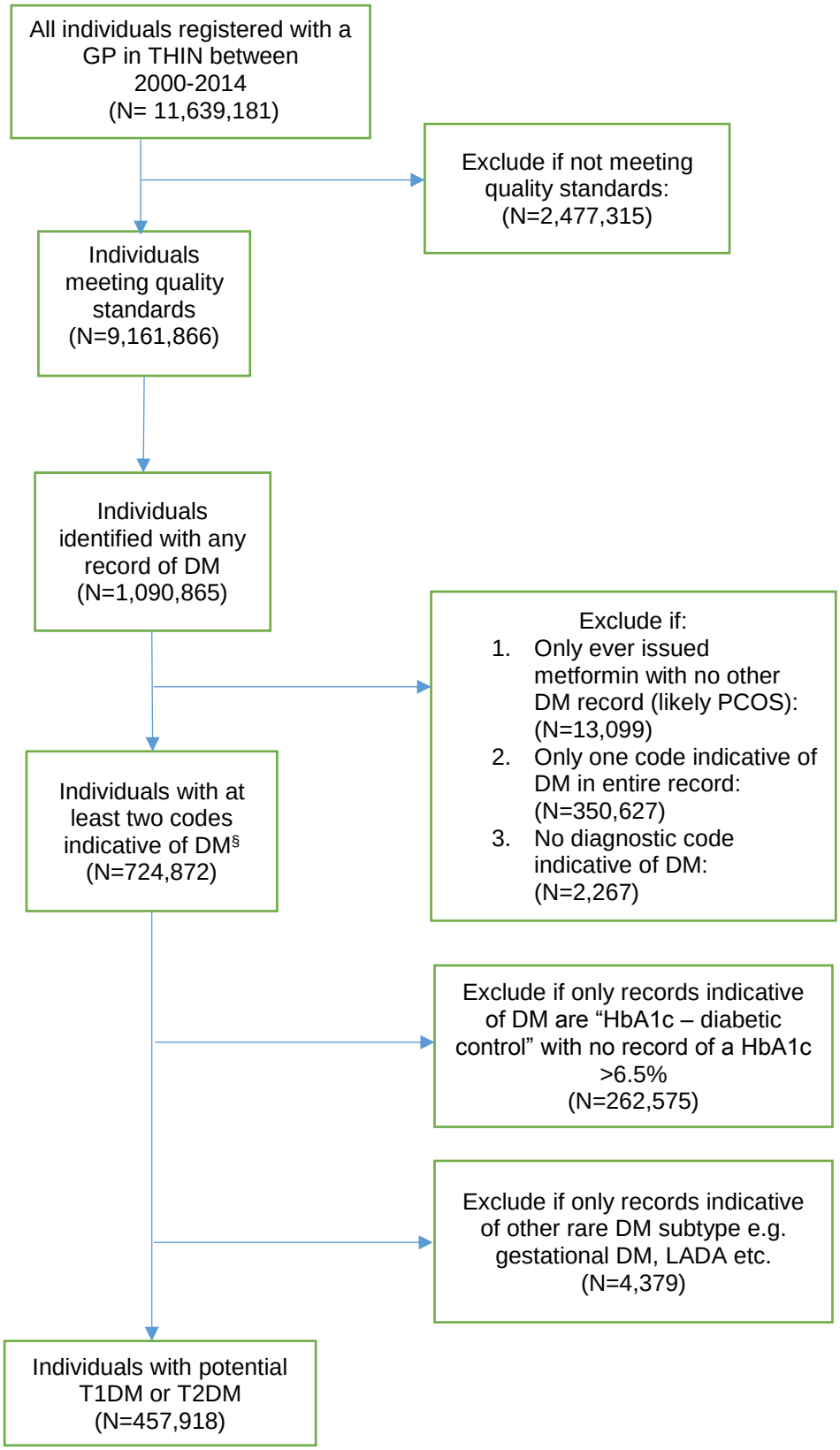


Figure 4.2 Flowchart for Algorithm 1: Identification of individuals with potential type 1 or type 2 diabetes mellitus

§Two codes must include at least one diagnostic Read code or ahdcode. THIN=The Health Improvement Network, DM=Diabetes Mellitus, PCOS=Polycystic Ovarian Syndrome, LADA=Latent Autoimmune Diabetes in Adults, T1DM=Type 1 Diabetes Mellitus, T2DM=Type 2 Diabetes Mellitus. Note: Figure taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 2).

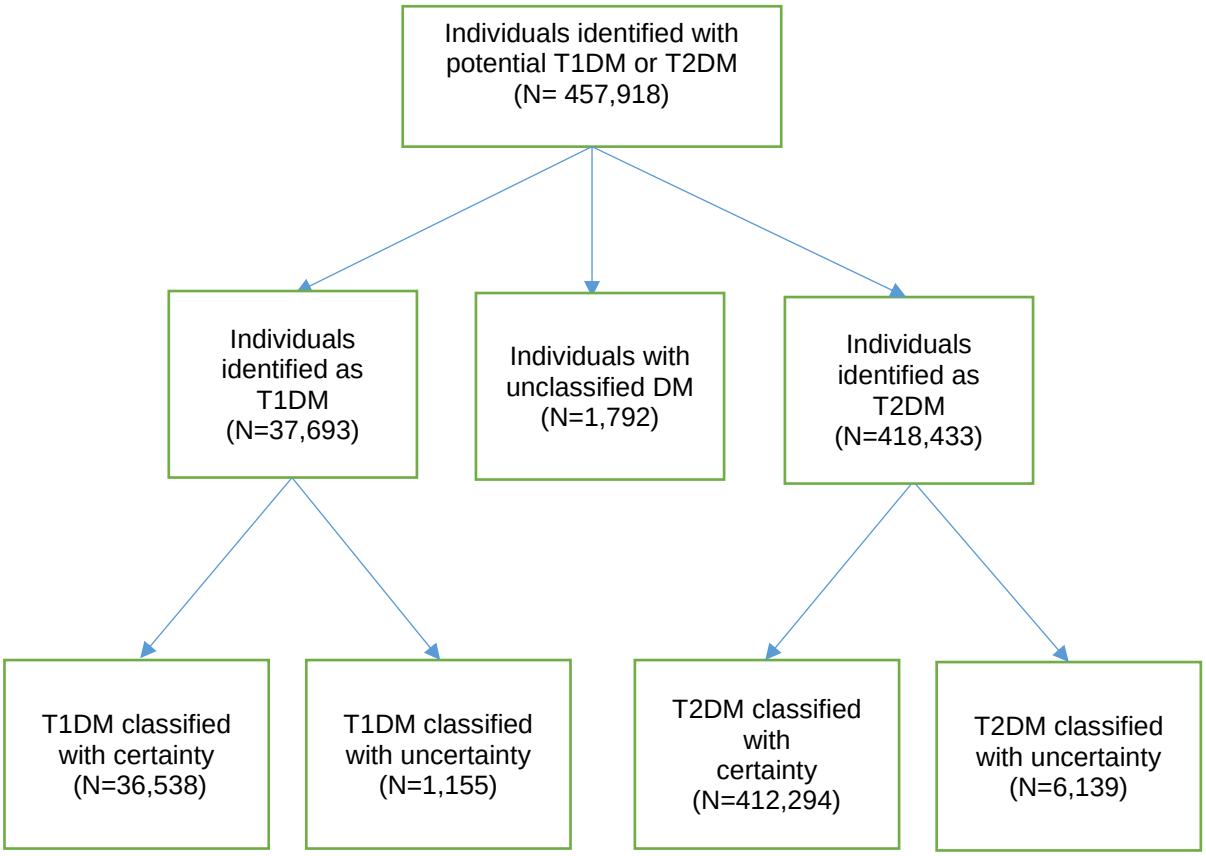


Figure 4.3 Flowchart for Algorithm 2: Classification of individuals with potential type 1 or type 2 diabetes mellitus
T1DM=Type 1 diabetes mellitus, T2DM=Type 2 diabetes mellitus
Note: Figure taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 2).

Individuals with type 2 diabetes mellitus met one of the following criteria:

1. A diagnostic code for T2DM only and any quantity of prescription for other anti-diabetic agents with or without insulin.
2. A diagnostic code for DM of any type and prescriptions for more than 6 months cumulatively of other anti-diabetic agents with or without insulin.
3. A diagnostic code for DM of any type and any quantity of prescription for other anti-diabetic agents with no insulin prescription.
4. A diagnostic code for T2DM or unspecific diagnostic codes and no prescribed treatment.
5. A diagnostic code for T1DM only and no prescribed treatment.*
6. A diagnosis of T2DM only or unspecific diagnostic codes, prescribed insulin only, a prevalent case and diagnosed with DM over the age of 35.*
7. Unspecific diagnostic codes, prescribed insulin with less than 6 months cumulatively of other anti-diabetic agents, a prevalent case and diagnosed with DM over the age of 35.*

*Individuals classified with uncertainty

Table 4.2 Algorithm for classification of individuals with DM as type 1 or type 2

Type assigned	Code type used	Treatment	Case type	Age at diagnosis	Number
Type 1	T1DM only	Insulin only	-	-	27,942
		Insulin + OAD<6m	-	-	1,922
	T2DM only	Insulin only	Incident	<35	150
				≥35	1,427
			Prevalent	<35	487
	Unspecific§	Insulin only	Incident	<35	890
				≥35	1,364
			Prevalent	<35	2,356
		Insulin + OAD<6m	Incident	<35	238*
				≥35	675*
			Prevalent	<35	242*
Total					37,693
Type 2	T1DM only	Insulin + OAD≥6m	-	-	3,745
		OAD<6m	Incident	<35	7
				≥35	13
			Prevalent	<35	8
				≥35	17
		OAD≥6m	-	-	107
		No treatment	-	-	611*
	T2DM only	Insulin	Prevalent	≥35	2,975*
		Insulin + OAD<6m	-	-	2,993
		Insulin + OAD≥6m	-	-	45,896
		OAD<6m	-	-	22,968
		OAD≥6m	-	-	202,865
		No treatment	-	-	70,266
	Unspecific§	Insulin only	Prevalent	≥35	2,043*
		Insulin + OAD<6m	Prevalent	≥35	510*
		Insulin +OAD≥6m	-	-	11,197
		OAD<6m	-	-	5,775
		OAD≥6m	-	-	11,319
		No treatment	-	-	35,118
Total					418,433
Unclassified	T1DM only	OAD<6m	Prevalent	¥	17
	T2DM only	Insulin only	Prevalent	¥	448
	Unspecific§	Insulin only	Prevalent	¥	1,059
		Insulin + OAD<6m	Prevalent	¥	268
Total					1,792

§Type 1 and type 2 diabetes mellitus codes or Non-specific codes

¥Age of diagnosis could not be confirmed

*Individuals classified with a degree of uncertainty.

T1DM=Type 1 diabetes mellitus, T2DM=Type 2 diabetes mellitus, OAD=Other anti-diabetics

Note: Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 2).

Uncertainty in classification

T1DM cases classified with uncertainty were those with a T2DM or unspecific code only and up to 6 months of other antidiabetics prescribed in addition to insulin. Though individuals with T1DM do all ultimately require insulin for survival, a small proportion have a slower onset of disease and may erroneously have other anti-diabetics prescribed while some residual pancreatic insulin production remains and diagnosis is unclear.[9] Furthermore, it is rare for T2DM individuals to be prescribed insulin rapidly after diagnosis. For these uncertain cases, I determined if they were incident DM cases and thus whether I had a full history of treatment for that individual. In addition, I also examined the age of diagnosis in cases where there was uncertainty. This is because individuals diagnosed under 35 and prescribed insulin were more likely to have T1DM.[9]

T2DM cases classified with uncertainty included individuals with T1DM codes only but not prescribed treatment, individuals with unspecific diagnostic codes and on insulin prescriptions (and none or less than 6 months of other anti-diabetics) and over the age of 35 at diagnosis.[9] Though it is rare for T2DM individuals to be managed on insulin alone or progress to needing insulin rapidly after treatment initiation,[7,9] given they were diagnosed over age of 35 and that these were prevalent cases that had a history of DM prior to registration that I had no data on, these were classified as T2DM cases but with uncertainty. These uncertain cases of T2DM collectively represented only 1.2% of the total T2DM cohort identified.

4.4.4.3 Validation

In the internal validation of 500 random individuals with DM, manual assignment of DM type based on clinical assessment of the entire electronic record available in THIN (reference standard) and algorithmic assignment led to equivalent classification in all instances.

4.4.5 Comparison of these algorithm with existing literature

In this study I describe algorithms to identify and classify individuals with T1DM and T2DM in a large UK primary care database and demonstrated that the vast majority of individuals can be classified with confidence; 36,538 (96.9%) individuals with T1DM and 412,294 (98.5%) individuals with T2DM.

Other algorithms have been previously developed in clinical studies to identify individuals with T2DM specifically,[102] and advise on how to distinguish T1DM and T2DM.[103] There was, however,

a lack of guidance on distinguishing between T1DM and T2DM in a general practice database such as THIN.

4.4.6 Strengths and Limitations of the algorithm

The main strength of these algorithms are that they identify and classify the majority of individuals with T1DM and T2DM with confidence and clearly outline individuals for whom classification is challenging and where it is not possible. This means that depending on the clinical question of interest, the diabetes cohort chosen for the study can be modified; for example by excluding individuals classified with uncertainty one can ensure greater confidence in classification in the cohort. Additionally, all codelists were independently generated by two researchers and reviewed clinically for accuracy and agreement.

Though, this algorithm is most suited for use in UK general practice databases such as THIN and CPRD (Clinical Practice Research Datalink), it can be adapted easily for use in epidemiological research for other settings. ICD-10 (International Classification of Diseases) codes or other hierarchical coding systems indicative of DM could be used instead of Read Codes while pharmacological therapy and thresholds for the age at diagnosis could be modified as necessary according to local treatment and monitoring guidelines.

The quality and outcomes framework introduced as part of the GP contract for the UK in 2004 brought in several indicators for DM to help improve disease management.[104] However as financial incentives were introduced for use of certain T1DM and T2DM specific codes, overzealous recording may have led to erroneous diagnoses.[103] The algorithms consider medications prescribed, HbA1c results, age of diagnosis and whether a case is incident or prevalent which will help reduce such errors

There are however some limitations to acknowledge. In this study I did not obtain external validation by comparison of the classification systems based on the algorithm to actual complete patient case notes. This would further strengthen the case for use of this algorithm. The sample size of 500 records for internal validation was chosen for feasibility purposes but given the significant size of the cohort, a larger sample size would have been preferable to ensure more accurate validation. Markers such as Body Mass Index (BMI) and ethnicity could have potentially been used as additional indicators for classification. BMI is generally higher among individuals with T2DM rather than T1DM,[105] while T2DM is known to be more prevalent among certain ethnic groups.[106] However given the variables I included already facilitated classification for 99.6% of the cohort, I did not investigate further.

Cases with only diagnostic codes related to rarer subtypes of DM such as maturity onset diabetes of the young, latent autoimmune diabetes in adults, drug-induced diabetes and gestational diabetes were excluded. However, this of course cannot guarantee that some miscoded and misdiagnosed cases did not enter the cohort.

Patient records in THIN are dynamic i.e. some individuals have been registered for much longer than others. People with only a short duration of registration may not have DM entered to their records or a sufficient time to be issued treatment for DM. Therefore varying record lengths can risk introducing bias. Therefore if the algorithm is applied to other datasets, it is worth noting that the longer and more homogenous the record lengths, the lower the risk of any such bias will be.

Finally, with recent recommendations by bodies such as the National Institute for Health and Care Excellence in 2015 to consider prescribing metformin for individuals with T1DM with higher BMI,[22] this algorithm will need to be adapted for use in future years. This could be achieved by further scrutinizing the records of individuals on metformin and insulins only for indicators that may help distinguish them as T1DM or T2DM such as diagnostic codes and age of diagnosis.[107]

4.5 Context of this chapter in overall work

In this chapter, I have described THIN and the generation of the T2DM cohort. In the next chapter, I will use individuals identified as having T2DM in this cohort to examine incidence, prevalence and prescribing patterns of the disease in UK primary care. This will help inform on how best to extract the cohort of individuals prescribed sitagliptin or sulphonylureas as add-on to metformin for the effectiveness studies later in the thesis. This chapter has also formed the basis of a published manuscript included in appendix for reference (Appendix H - Citation 2).

Chapter 5 Trends in recording of diagnosis and prescribing in type 2 diabetes mellitus

5.1 Chapter Overview

In this chapter, I will further explore the Type 2 Diabetes Mellitus (T2DM) cohort generated in Chapter 4 and use it to determine how the recording of diagnosis of T2DM has changed over time in THIN and compare my findings with current literature. I will also examine prescribing patterns for anti-diabetic medication between 2000 and 2013. This will enable me to get a better understanding of how I can extract my cohort prescribed sitagliptin and sulphonylureas as add-on to metformin and help provide insight into the design of the cohort studies later in this thesis.

5.2 Study background

Managing T2DM and its complications accounts for close to 10% of the entire NHS budget in the UK.[35] Significant developments over the last decade have influenced both diagnosis and pharmacological treatment of T2DM in the UK. In 2000, for example, implementation of the revised World Health Organisation diabetes diagnostic criteria led to a lower fasting plasma glucose threshold of 7.0mmol/l being used for diagnosis rather than 7.8 mmol/l.[108] This is known to have led to a significant rise in new cases of T2DM. Several new therapies have also emerged in the past decade such as gliptins making the choice of suitable anti-diabetic regimens challenging.[109] Periodic guidance from national and international bodies such as National Institute for Health and Care Excellence (NICE), American Diabetes Association (ADA) and European Association of Diabetics (EASD) in particular, have offered more objective advice to prescribers.[24,110] However, without analysis of "real world" data, one cannot be fully sure how these treatments are actually being prescribed within the UK setting.

The aim of this study was to investigate how the incidence and prevalence of T2DM diagnoses as well as prescribing patterns have changed between 2000 and 2013 using data from The Health Improvement Network (THIN) primary care database.

5.2.1 Study Objectives

1. Investigate changes in incidence of T2DM
2. Investigate changes in prevalence of T2DM

3. Investigate changes in prescribing of anti-diabetic agents among newly diagnosed T2DM individuals for first line and add-on therapy as well as investigating prevalent use of these medicines.

5.3 Methods

5.3.1 Study Population and Period

All individuals aged 0-99 years who were permanently registered with a general practice contributing data to THIN between 2000 and 2013 were included in this study. All data was extracted from practices which met the acceptable mortality reporting (AMR) and acceptable computer usage (ACU) standards in THIN as described in Chapter 4 (Section 4.3.4).[91,92]

The algorithms used for generation of the T2DM cohort were described in detail in Chapter 4 (Section 4.4). The first record of any of the following was considered the date of diagnosis for T2DM; (1) a diagnostic code for diabetes (2) supporting evidence of diabetes e.g. screening for diabetic retinopathy or (3) treatment for diabetes. Scientific approval to undertake this study was obtained from CMD Medical Research's Scientific Review Committee in February 2015. (SRC Reference Number: 15-011).

5.3.2 Definition of Main Outcomes in Study

5.3.2.1 Incidence of T2DM

The date on which the first recording of T2DM was made was classified as the date of diagnosis. Therefore, my use of the term incidence with respect to T2DM in this study refers to the first record of T2DM to appear in an individual's electronic primary care record in the THIN database. Individuals who had their first recording of T2DM made within the first nine months of practice registration were not considered incident cases as these were more likely to be prevalent cases as established in previous work completed by Mamtani et al as detailed in Chapter 4 (Section 4.4.3.2).[111]

5.3.2.2 Prevalence of T2DM

For the analysis on prevalence of T2DM by calendar year, I included as the numerator all individuals who had a record of T2DM on or before 1st January in the given year and as the denominator, I included all individuals registered to a general practice on or by 1st January in that given year.

To estimate prevalence by age, gender and social deprivation, I identified numerators and denominators as described above. Given age invariably changed with time, I focused on data

from 2013 only and calculated age on 1st January 2013. Gender and social deprivation were considered fixed variables.

5.3.2.3 Prescription patterns Analysis

The prevalence of use of different anti-diabetic medicines for T2DM was also compared across the time period 2000-2013. I categorised anti-diabetic medications by therapeutic class into ten groups; metformin, sulphonylureas, insulins, thiazolidinediones, gliptins, sitagliptin only, GLP-1 analogues, SGLT-2 inhibitors, meglitinides and acarbose. Prevalence of prescribed medications was calculated by dividing the total number of individuals issued a prescription for a particular anti-diabetic medication class by the total number of individuals issued any anti-diabetic medication in that calendar year.

Individuals with an incident recording of T2DM between 2000-2013 were analysed to examine how prescribing patterns may have changed over time for newly diagnosed T2DM specifically. I determined what anti-diabetic drug was prescribed for initiating treatment in T2DM and then examined what anti-diabetic agents were typically added on by prescribers at a later stage (when the disease had progressed further).

5.3.3 Statistical Analyses

The overall crude incidence of T2DM was estimated per 1000 person years at risk (PYAR). This was determined by totalling the number of individuals with a first recording of T2DM between 2000-2013 and dividing by the total person years of follow-up for all individual records for this period. Crude incidence rates by age, gender, social deprivation (Townsend quintile) and calendar year were also determined by restricting the person years of follow-up to the respective category in question. Person time was measured from the latest of: the date of registration plus nine months or 1st January 2000 to the earliest of: date of first recording of T2DM, date of death, date individual left the practice, last date of data collection from that practice or 31st Dec 2013. Multivariable Poisson regression analysis with (log) person time as an offset was used to analyse changes in incidence by age, gender, social deprivation and calendar year whilst controlling for the other respective variables.

The crude prevalence of T2DM for each year was calculated by dividing the number of all individuals recorded as having T2DM on or before 1st January of that year by the total number of individuals registered to a general practice on or by 1st January of that year. Multivariable Poisson regression analysis was used to estimate prevalence ratios of T2DM by year as well as mutually adjusted prevalence ratios for age, gender and social deprivation for 2013 only.

To investigate the impact of clustering by practice, multilevel random intercept models were compared to all the standard Poisson models used, however clustering was not found to be significant in any instance. Likelihood ratio tests were used to explore the significance of interaction between variables.

Prescription records were also analysed to describe changes over time in prescribing habits in primary care. The percentage of individuals with T2DM prescribed different anti-diabetic therapies for ever-use (prevalence), first line use and as add-on therapy was determined for each calendar year and 95% confidence intervals were calculated.

5.4 Results

In total, 406,344 individuals with T2DM were identified and among these 203,639 were incident cases of T2DM between 2000 and 2013.

5.4.1 Incidence of T2DM

The incidence of T2DM increased from 3.69 per 1000 person-years at risk (PYAR) (95% CI 3.58 to 3.81) in 2000 to 3.99 per 1000 PYAR (95% CI 3.90 to 4.08) in 2013 for men; and from 3.06 per 1000 PYAR (95% CI 2.95 to 3.17) to 3.73 per 1000 PYAR (95% CI 3.65 to 3.82) in 2013 for women (Table 5.1). Incidence peaked in 2004 for both men; 4.80 per 1000 PYAR (95% CI 4.70 to 4.90) and women; 4.28 per 1000 PYAR (95% CI 4.19 to 4.38). There was a significant interaction between age and gender ($p<0.001$), hence all results are presented separately for men and women in Table 5.1. Women had a lower incidence of T2DM than men [Incidence rate ratios (IRR) 0.81 (95% CI 0.80 to 0.82)] and individuals from the most socially deprived areas had a significantly higher incidence than individuals from the least deprived areas [Townsend Quintile 5 vs Townsend Quintile 1; (IRR 1.57 95% CI 1.54 to 1.60) for men and (IRR 1.92 95% CI 1.88 to 1.97) for women]. In general, incidence of T2DM increased with age peaking between 70-79 years.

5.4.2 Prevalence of T2DM

Prevalence of T2DM in 2013 was 5.11 per 100 women and 5.91 per 100 men [Prevalence Ratio (PR) 0.79, 95% CI 0.79 to 0.80)] (Table 5.2) and highest among individuals in the most deprived areas [Townsend quintile 5 vs Townsend quintile 1; (PR 1.75, 95% CI 1.73 to 1.78)]. The prevalence increased with age. The highest prevalence for T2DM was seen in the 80–89 years age band: 19.29 per 100 individuals (95% CI 19.11 to 19.46). In comparison to individuals aged

40–49 years, the adjusted prevalence ratio for 80–89 years age band was 5.69, (95% CI 5.60 to 5.78) (Table 5.2).

Table 5.1 Incidence of type 2 diabetes mellitus by socio-demographic factors and year

	Incidence of type 2 diabetes Rate per 1000 PYAR (95% CI)		Adjusted IRR (95% CI)*	
	Men	**Women**	**Men**	**Women**
Overall	4.19 (4.17 to 4.21)	3.72 (3.70 to 3.74)	1	0.81 (0.80 to 0.82)
Age, years				
0-9	0.04 (0.03 to 0.05)	0.04 (0.04 to 0.05)	0.01 (0.01 to 0.01)	0.01 (0.01 to 0.02)
10-19	0.11 (0.10 to 0.13)	0.28 (0.26 to 0.30)	0.03 (0.03 to 0.03)	0.09 (0.09 to 0.10)
20-29	0.36 (0.34 to 0.38)	1.15 (1.11 to 1.19)	0.09 (0.08 to 0.09)	0.37 (0.35 to 0.38)
30-39	1.36 (1.32 to 1.39)	1.91 (1.86 to 1.95)	0.33 (0.32 to 0.34)	0.63 (0.61 to 0.65)
40-49	4.02 (3.97 to 4.08)	3.00 (2.95 to 3.05)	1	1
50-59	7.86 (7.78 to 7.95)	5.43 (5.36 to 5.50)	1.98 (1.94 to 2.01)	1.83 (1.79 to 1.87)
60-69	11.87 (11.74 to 12.00)	8.48 (8.38 to 8.59)	2.98 (2.92 to 3.03)	2.84 (2.78 to 2.90)
70-79	12.68 (12.51 to 12.85)	10.32 (10.19 to 10.46)	3.18 (3.12 to 3.25)	3.43 (3.35 to 3.50)
80-89	9.08 (8.87 to 9.30)	8.00 (7.84 to 8.15)	2.26 (2.19 to 2.32)	2.57 (2.50 to 2.64)
90-99	5.96 (5.49 to 6.46)	4.55 (4.31 to 4.81)	1.48 (1.36 to 1.61)	1.45 (1.37 to 1.54)
Townsend Quintile				
1	3.86 (3.82 to 3.91)	2.99 (2.95 to 3.03)	1	1
2	4.19 (4.14 to 4.25)	3.50 (3.46 to 3.55)	1.09 (1.07 to 1.11)	1.15 (1.13 to 1.17)
3	4.29 (4.24 to 4.34)	3.86 (3.81 to 3.91)	1.25 (1.23 to 1.27)	1.37 (1.35 to 1.40)
4	4.47 (4.41 to 4.53)	4.32 (4.26 to 4.38)	1.42 (1.40 to 1.45)	1.63 (1.60 to 1.66)
5	4.62 (4.55 to 4.70)	4.75 (4.68 to 4.83)	1.57 (1.54 to 1.60)	1.92 (1.88 to 1.97)
Year				
2000	3.69 (3.58 to 3.81)	3.06 (2.95 to 3.17)	1	1
2001	4.20 (4.08 to 4.31)	3.52 (3.42 to 3.63)	1.14 (1.09 to 1.19)	1.16 (1.1 to 1.21)
2002	4.48 (4.37 to 4.59)	3.73 (3.63 to 3.83)	1.22 (1.17 to 1.27)	1.24 (1.18 to 1.29)
2003	4.52 (4.41 to 4.62)	3.96 (3.87 to 4.06)	1.24 (1.19 to 1.29)	1.32 (1.27 to 1.38)
2004	4.80 (4.70 to 4.90)	4.28 (4.19 to 4.38)	1.32 (1.27 to 1.37)	1.44 (1.38 to 1.50)
2005	4.56 (4.46 to 4.66)	4.04 (3.95 to 4.13)	1.25 (1.20 to 1.30)	1.36 (1.30 to 1.42)
2006	4.52 (4.42 to 4.61)	3.93 (3.84 to 4.02)	1.24 (1.19 to 1.29)	1.33 (1.27 to 1.39)
2007	4.62 (4.52 to 4.72)	4.07 (3.98 to 4.16)	1.26 (1.22 to 1.31)	1.37 (1.32 to 1.43)
2008	4.62 (4.52 to 4.71)	4.06 (3.97 to 4.15)	1.26 (1.21 to 1.31)	1.37 (1.32 to 1.43)
2009	4.71 (4.61 to 4.80)	4.26 (4.18 to 4.36)	1.29 (1.24 to 1.34)	1.45 (1.39 to 1.51)

	Incidence of type 2 diabetes Rate per 1000 PYAR (95% CI)		Adjusted IRR (95% CI)*	
	Men	**Women**	**Men**	**Women**
2010	4.48 (4.39 to 4.58)	4.10 (4.01 to 4.19)	1.23 (1.18 to 1.28)	1.40 (1.34 to 1.46)
2011	4.26 (4.17 to 4.35)	3.97 (3.88 to 4.05)	1.16 (1.12 to 1.21)	1.35 (1.30 to 1.41)
2012	4.40 (4.31 to 4.49)	4.00 (3.91 to 4.09)	1.20 (1.16 to 1.25)	1.37 (1.31 to 1.43)
2013	3.99 (3.90 to 4.08)	3.73 (3.65 to 3.82)	1.09 (1.05 to 1.13)	1.28 (1.22 to 1.33)

*Adjusted for other variables considered; ageband, Townsend quintile, calendar year respectively
Note: I have presented incidence stratified by gender due to significant age-gender interaction (likelihood ratio test, p<0.001)
Note 2: For figure displaying data above consult Appendix C (Supplementary Figure 5A1)
Note 3: Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 1).

Table 5.2 Prevalence of type 2 diabetes mellitus per 100 individuals by calendar year and by socio-demographic factors for 2013 only

Prevalence of type 2 diabetes in 2013 by socio-demographic factors		
	Percentage Prevalence (95% CI)	**Adjusted PR (95% CI)***
Gender		
Men	5.91 (5.88 to 5.94)	1
Woman	5.11 (5.08 to 5.14)	0.79 (0.79 to 0.80)
Age, years		
0-9	0.03 (0.02 to 0.03)	0.01 (0.01 to 0.01)
10-19	0.14 (0.13 to 0.15)	0.03 (0.03 to 0.04)
20-29	0.60 (0.58 to 0.62)	0.15 (0.15 to 0.16)
30-39	1.65 (1.62 to 1.68)	0.42 (0.41 to 0.43)
40-49	3.70 (3.66 to 3.75)	1
50-59	7.76 (7.69 to 7.82)	2.16 (2.13 to 2.20)
60-69	12.95 (12.85 to 13.04)	3.73 (3.67 to 3.79)
70-79	18.75 (18.61 to 18.88)	5.48 (5.40 to 5.56)
80-89	19.29 (19.11 to 19.46)	5.69 (5.60 to 5.78)
90-99	13.44 (13.14 to 13.75)	4.07 (3.96 to 4.19)
Townsend Quintile		
1	5.00 (4.95 to 5.04)	1
2	5.52 (5.47 to 5.56)	1.11 (1.10 to 1.13)
3	5.67 (5.63 to 5.72)	1.31 (1.30 to 1.33)
4	5.94 (5.89 to 5.99)	1.53 (1.51 to 1.54)
5	6.25 (6.19 to 6.31)	1.75 (1.73 to 1.78)
Annual Prevalence of Type 2 Diabetes between 2000-2013		
	Percentage Prevalence (95% CI)	**Unadjusted PR (95% CI)**
Year		
2000	2.39 (2.37 to 2.41)	1
2001	2.60 (2.58 to 2.62)	1.10 (1.08 to 1.11)
2002	2.84 (2.83 to 2.86)	1.20 (1.19 to 1.21)
2003	3.11 (3.09 to 3.13)	1.32 (1.30 to 1.33)
2004	3.40 (3.38 to 3.42)	1.44 (1.43 to 1.45)
2005	3.66 (3.64 to 3.67)	1.55 (1.53 to 1.56)
2006	3.88 (3.86 to 3.90)	1.64 (1.63 to 1.65)
2007	4.10 (4.08 to 4.12)	1.73 (1.71 to 1.74)
2008	4.33 (4.32 to 4.35)	1.82 (1.81 to 1.84)
2009	4.56 (4.54 to 4.58)	1.91 (1.90 to 1.93)
2010	4.78 (4.76 to 4.80)	2.01 (1.99 to 2.02)
2011	4.98 (4.96 to 5.00)	2.08 (2.07 to 2.10)
2012	5.17 (5.15 to 5.19)	2.16 (2.14 to 2.18)
2013	5.32 (5.30 to 5.34)	2.21 (2.19 to 2.23)

*PR (prevalence ratios) mutually adjusted for other variables considered; gender, age band, Townsend quintile respectively

Note: For figure displaying prevalence by calendar years above consult Appendix C (Supplementary Figure 5A2)

Note 2: Table taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 1).

5.4.3 Prescribing in T2DM

5.4.3.1 Prevalence of anti-diabetic medicine prescribed in individuals with T2DM

A total of 305,765 (75.2%) individuals out of 406,344 with T2DM were prescribed anti-diabetic medication. The prescribing of metformin rose from 55.4% (95% CI 55.0 to 55.8) in 2000 to 83.6% (95% CI 83.4 to 83.8) in 2013, whilst the prescribing of sulphonylureas decreased from 64.8%

(95% CI 64.3 to 65.2) in 2000 to 41.4% (95% CI 41.1 to 41.7) of treated individuals with T2DM by 2013 (Figure 5.1).

Prescribing of thiazolidinediones peaked in 2007 at 16.0% (95% CI 15.8 to 16.3) while that of gliptins peaked in 2013 at 15.4% (95% CI 15.2 to 15.7) of all treated individuals (Figure 5.1). Sitagliptin accounted for the vast majority of these gliptin prescriptions; 11.6% (95% CI 11.4 to 11.8). Prescribing of acarbose and meglitinides declined and were prescribed in <0.5% of T2DM individuals on anti-diabetic medications by 2013. Insulin prescribing however remained stable with 20-24% of treated individuals annually prescribed insulin between 2000-2013.

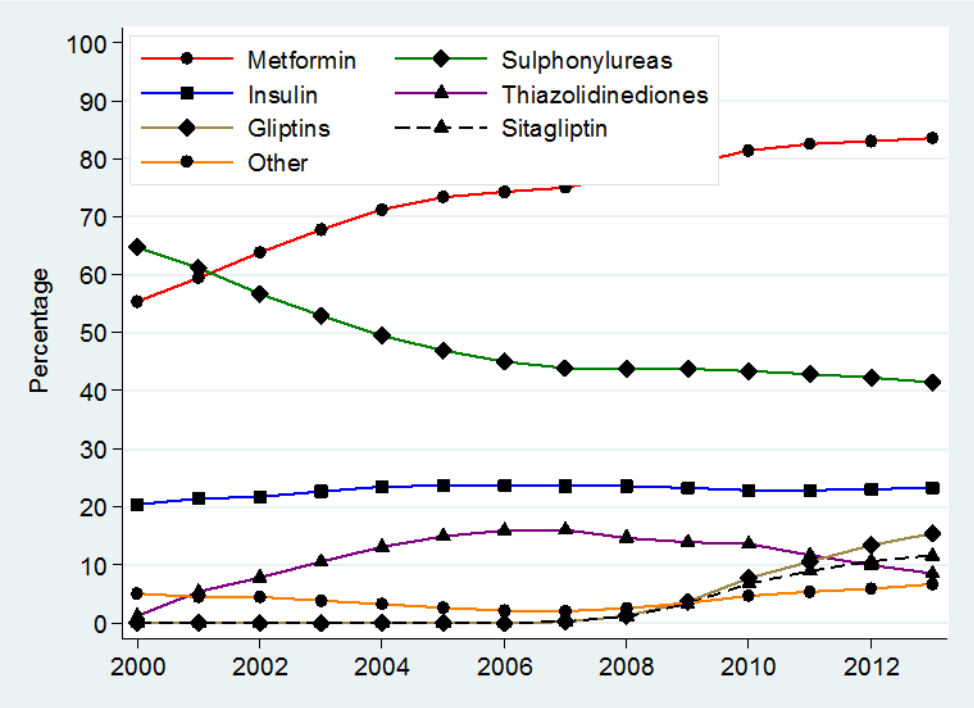


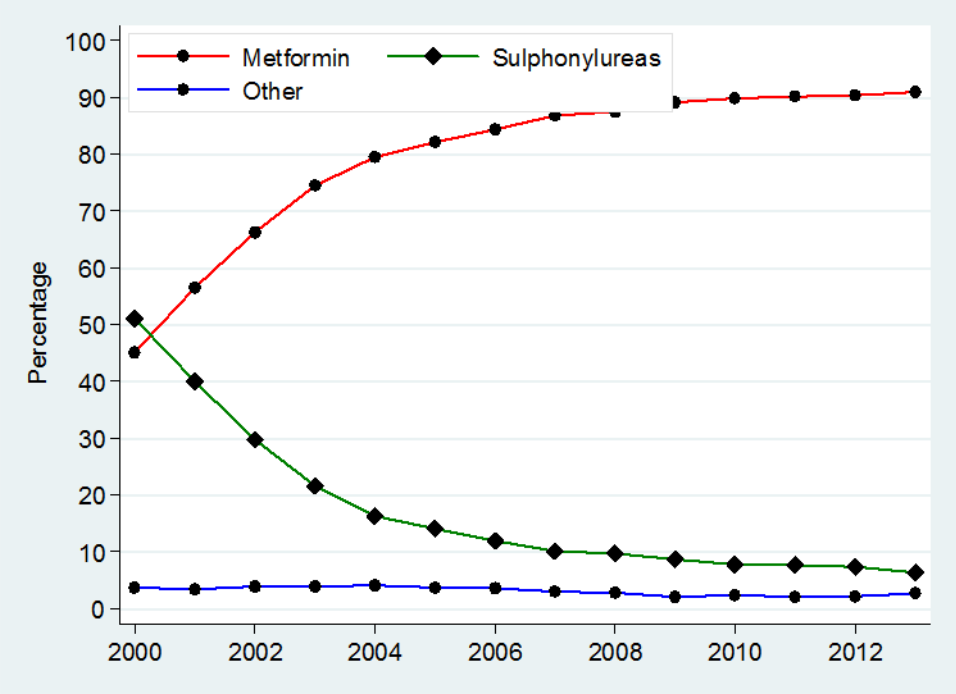
Figure 5.1 Prevalence of prescribing of different anti-diabetic classes among all individuals with type 2 diabetes mellitus on medication

Other=Sum of prevalence of Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors.
Note: For detailed values of point estimates and confidence intervals, please consult Appendix C (Supplementary Table 5A1). Note 2: Figure taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 1).

5.4.3.2 Medicines used to initiate treatment in newly diagnosed individuals with T2DM

A total of 127,523 (62.6%) of 203,639 newly diagnosed individuals with T2DM identified were initiated on treatment between 2000-2013. In 2000, 51.1% (95% CI 49.2 to 53.0) were initiated on sulphonylureas and 45.1% (95% CI 43.2 to 47.1) on metformin (Figure 5.2). Use of metformin as first-line therapy increased annually and by 2013, 91.0% (95% CI 90.5 to 91.5) of individuals newly diagnosed with T2DM requiring treatment were being initiated on this therapy. However, sulphonylurea usage as first line therapy declined by 2013; to 6.3% (95% CI 5.9 to 6.8). Few individuals with newly diagnosed T2DM were prescribed insulin first-line in 2013; 1.7% (95% CI

1.4 to 1.9). Use of thiazolidinediones as first-line therapy remained low and peaked in 2004 [1.1% (95% CI 0.9 to 1.3)]. Other anti-diabetic therapies such as gliptins, GLP-1 analogues, acarbose or meglitinides were used very rarely as first line treatments (<1%) in any calendar year.



5.4.3.3 Medicines prescribed as add-on agents after initiation with metformin in individuals with newly diagnosed T2DM between 2000-2013

Figure 5.2 Prevalence of prescribing of different anti-diabetic classes used as first-line treatment in newly diagnosed individuals with type 2 diabetes mellitus.
Other=Sum of prevalence of Insulins, Thiazolidinediones, Gliptins, Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors.
Note: For detailed values of point estimates, please consult please consult Appendix C (Supplementary Table 5A2). Note 2: Figure taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 1).

Sulphonylureas were annually the most common add-on therapy used in newly diagnosed individuals with T2DM between 2000-2013 already on metformin (Figure 5.3). However, sulphonylureas use as an add-on declined from 75.9% (95% CI 72.6 to 79.3) in 2000 to 61.7% (95% CI 59.2 to 64.2) in 2013. The use of thiazolidinedione as add-on therapy to metformin peaked in 2002 at 26.9% (95% CI 25.0 to 28.8); after which prescribing declined to 1.9% (95% CI 1.2 to 2.7) by 2013.

Gliptins have become the second most common class of anti-diabetic added to metformin therapy with 26.9% (95% CI 24.7 to 29.2) in 2013 with sitagliptin accounting for 16.5% (95% CI 14.6 to 18.4). In terms of individuals, this meant that out of 5,552 individuals who had a gliptin added to metformin between 2000-2013, 4,049 (72.9%) were prescribed sitagliptin. Other anti-diabetic therapies were far less commonly added on (Figure 5.3).

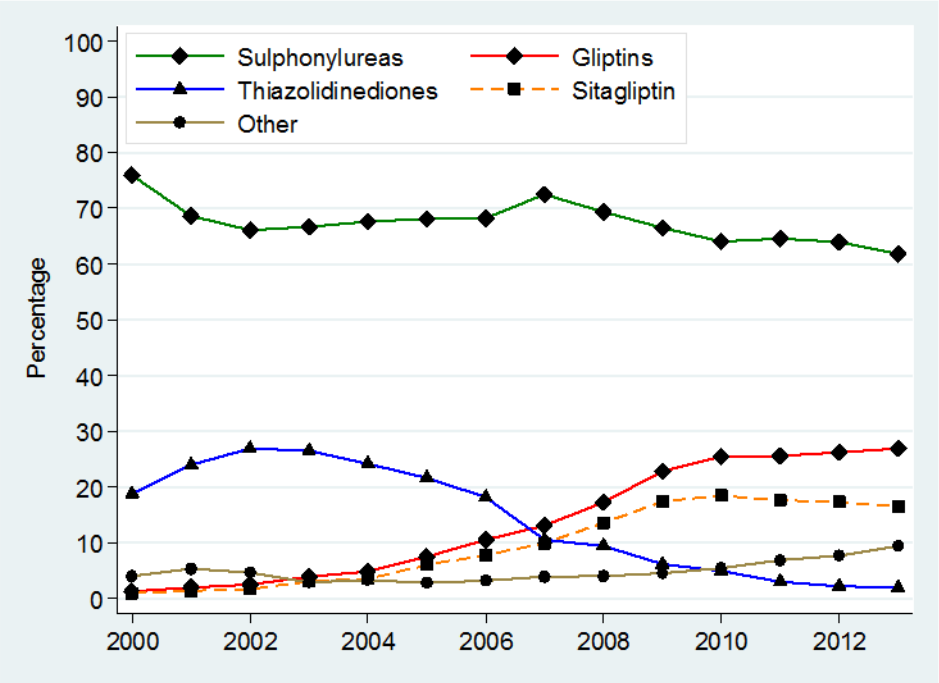


Figure 5.3 Prevalence of prescribing of different anti-diabetic classes in individuals with type 2 diabetes as add-on to metformin
Other=Sum of prevalence of Insulins, Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors detailed individually in smaller graph.
Note: For detailed figures on point estimates and confidence intervals, please consult Appendix C (Supplementary Table 5A3). Note 2: Figure taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 1).

5.4.3.4 Medicines prescribed as add-on agents after initiation with sulphonylureas in individuals with newly diagnosed T2DM between 2000-2013

Metformin was the most common treatment added on to newly diagnosed individuals with T2DM between 2000-2013 who were already on sulphonylureas (Figure 5.4). 89.8% (95% CI 87.7 to 92.0) of individuals diagnosed in 2000 went on to have metformin add-on therapy after sulphonylureas while 79.9% (95% CI 74.8 to 85.0) were prescribed metformin in 2013.

Insulins was the second most common add-on therapy to sulphonylureas, accounting for 13.4% (95% CI 9.1 to 17.7) in 2013 (Figure 5.4). Thiazolidinediones and gliptins were the third and fourth most common add-on therapies respectively. In terms of individuals prescribed gliptins, this meant that out of 168 individuals who had a gliptin added to sulphonylureas between 2000-2013, 105 (62.5%) were prescribed sitagliptin.

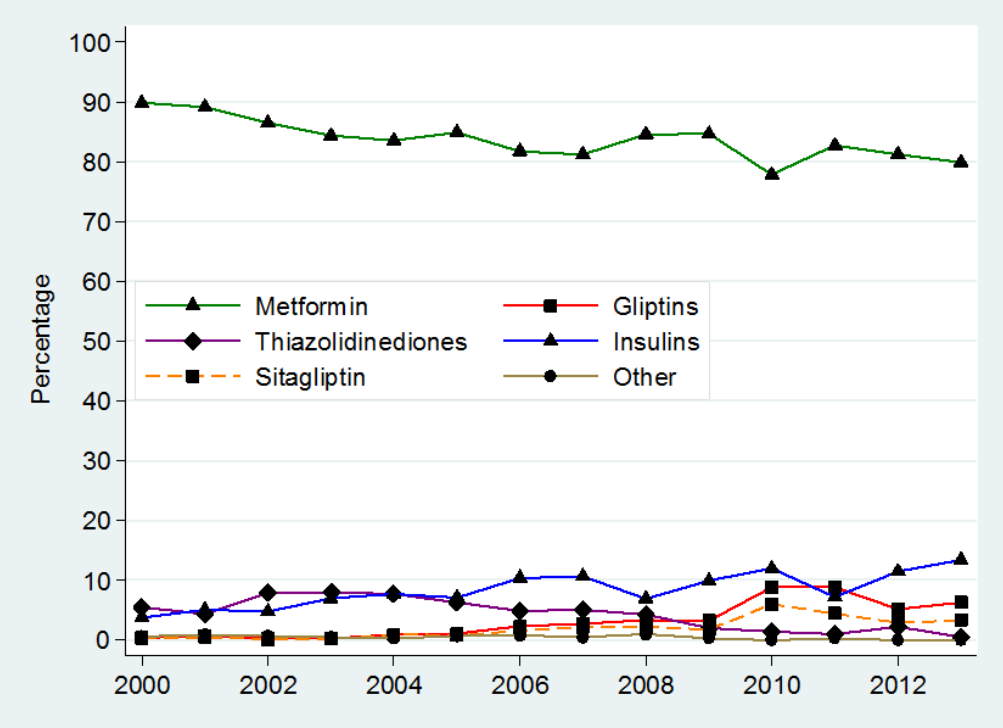


Figure 5.4 Prevalence of prescribing of different anti-diabetic classes in individuals with type 2 diabetes as add-on to sulphonylureas.
*Other=Sum of prevalence of Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors.
Note: For detailed figures on point estimates and confidence intervals, please consult Appendix C (Supplementary Table 5A4). Note 2: Figure taken from published manuscript by *Sharma et al* included in full in appendix for reference (Appendix H - Citation 1).

5.5 Discussion

5.5.1 Summary of Results

The incidence of T2DM in UK primary care rose significantly between 2000 and 2005 after which it stabilised around 3.99 per 1000 PYAR in men and 3.73 per 1000 PYAR in women by 2013. Data from 2013 showed women were 21% less likely to have T2DM than men and those who were most socially deprived were 75% more likely to have T2DM, as compared to those least deprived. Individuals aged 80–89 years had the highest adjusted prevalence of T2DM, which was nearly six times higher than individuals aged 40–49 years. Prescribing for T2DM also changed considerably over the study with metformin rising to account for 91.0% of first line therapy among newly diagnosed individuals with T2DM and 79.9% of add on therapy for individuals prescribed sulphonylureas by 2013. Use of gliptin therapy, largely sitagliptin, also increased and was used as an add-on in 26.9% of metformin treated individuals; while insulin use increased and was prescribed as an add-on in 13.4% of individuals after sulphonylureas by 2013.

5.5.2 Comparison with existing literature

The incidence of T2DM observed in this study is highly comparable (overlapping estimates) to incidence data that has been published previously in 2 studies examining incidence by Gonzalez et al in 2009 and Holden et al in 2013 respectively.[102,112] Previous studies were restricted to analysing the period prior to 2010, this study includes data up to 2013. The initial rise in incidence between 2000 and 2005 and plateau thereafter may be explained by the lowering of plasma glucose threshold for diagnosis of DM in 2000.[108] The increase in incidence observed in 2004 in this study could also relate to the introduction of incentivised payments in the UK as part of the quality and outcomes framework for better monitoring of individuals with T2DM.[93] Women were at greater risk of developing T2DM relative to men between the ages of 10-40 years, in keeping with other published work;[102] after this age, rates increased more significantly in men. Individuals from the most socially deprived areas in this study were at greatest risk of developing the disease. This is of concern as a study in the US has shown a strong association between socioeconomic status and diabetes related mortality.[113]

The rise in prevalence of T2DM described in this study was highly similar to that reported by Diabetes UK and the International Diabetes Federation in 2013.[114-116] Prevalence rates of T2DM observed in this study in the UK were also similar to what has been observed in Denmark and Sweden but lower than that observed in Germany and the US, particularly for recent years.[3,117]

Similar studies on prescribing conducted with smaller cohorts in the US have shown anti-diabetic prescribing choices to be quite different. For example in a US cohort study on data between 2009-2013 (n=15,516), 57.8% of individuals with T2DM initiated therapy with metformin, 23.0% with sulphonylureas, 13.1% with gliptins and 6.1% with thiazolidinediones,[118] while the corresponding percentages in this study (n=57,518) for same period 2009-2013 were; 90.0%, 7.6%, 0.4% and 0.1% respectively. This significant selection of metformin over other therapies in the United Kingdom suggests an adherence, particularly for treatment initiation, to cost-effective care as published via periodic updates by NICE.[22] This reliance on metformin for first line therapy has also been evident in other studies conducted across Europe in Germany and Denmark in particular.[21]

Metformin use increased steadily from 2000 and was prescribed to 91% of newly diagnosed individuals with T2DM requiring treatment in 2013. In 2000, metformin was recommended by NICE for use first-line in obese individuals with T2DM only, while non-obese individuals were still being recommended sulphonylureas and insulins.[119] However, by 2005, metformin was the

recommended first-line treatment choice by all major diabetes bodies[24,110] as it is in general, well tolerated apart from initial gastrointestinal adverse effects, does not induce weight gain or hypoglycaemia and was the only diabetic treatment found to have a long term benefit in reducing cardiovascular risks and organ damage.[24,120]

Use of sulphonylureas as a first line agent was found to have declined among newly diagnosed individuals with T2DM in keeping with published clinical guidance.[24,110] This decline may also be explained by the availability of more treatment options, the risk of weight gain and hypoglycaemia attributed to this class of drugs; and due to the absence of evidence that sulphonylureas reduced long-term complications of diabetes.[121,122] Nevertheless, 61.7% of individuals with T2DM diagnosed in 2013, still had sulphonylureas added to their metformin treatment.

From their emergence in 2006 to the end of 2013, gliptins have rarely been used as first-line therapy in newly diagnosed individuals with T2DM. However, their usage as add-on therapy to metformin in particular, has risen rapidly, as an alternative to sulphonylureas.[123,124] Closer analysis confirmed that in the UK setting, sitagliptin was by far the most common gliptin prescribed accounting for 72.9% (4,049) of the 5,552 individuals in this cohort that had a gliptin added to metformin.

Glucagon-like peptide 1 (GLP-1) analogues were the first anti-diabetic treatments to become available that could induce weight loss, however this study has shown that prescribing in UK primary care particularly as add-on therapy after metformin remains low (1.1%). This is in contrast to prescribing in Denmark where a study examining data for a similar period (2000-2012) provided evidence that nearly 6% of individuals with T2DM on metformin had GLP-1 analogues added on.[65]

A decline in thiazolidinedione prescribing after 2003 was observed in response to an increasing awareness of adverse effects of these drugs such as cardiotoxicity, highlighted in safety alerts for rosiglitazone by regulatory agencies in 2007.[125] Additionally, risks of weight gain, fractures, bladder cancer and hypoglycaemias still exist among currently licensed thiazolidinediones which may explain their limited use despite evident efficacy.[30]

A small percentage of newly diagnosed individuals with T2DM (1.7%) are still being initiated on insulin and a growing number are having insulin prescribed as add-on therapy. Though current guidance does not support early introduction of insulin, some studies have demonstrated a benefit.[33]

5.5.3 Strengths and Limitations of this study

This is the first study to detail changes in recording of diagnoses as well as prescribing for T2DM using UK primary care data between 2000 and 2013. I have also provided insight into factors that may have driven these changes. Furthermore, THIN has been shown to be a particularly suitable database for drug utilization work.[86] There are however certain limitations to highlight. Though the algorithm for identification of individuals with T2DM utilized several variables in addition to diagnostic codes such as treatment and time of diagnosis, there still remains a risk of some misclassification of T2DM as I highlighted in Chapter 4 (Section 4.4.6). Prevalence of T2DM was calculated as point prevalence using a denominator of those registered with a THIN affiliated practice on the 1st January of each calendar year studied. The limitations with this method of calculating prevalence (though it is the most common approach employed in database research) is that it means that some individuals included in the denominator will inevitably have a very short duration of practice registration, meaning they may not have sufficient time for all their diagnosis to be entered and thus the numerator (number of cases of diabetes mellitus) may be underestimated. As T2DM is a serious chronic condition, usually requiring medication it is more likely to be entered at time of registration or soon afterwards supported by the fact our estimates compared favourably with other published work. Nevertheless, this is a limitation with using such primary care databases for prevalence calculation and must be acknowledged. Also, this study did not measure prescribing of anti-diabetic medicines in secondary care, however, it is well established that the majority of prescribing for T2DM is undertaken in primary care within the UK. Variation in dosages or between drugs within the same therapeutic class except in the case of sitagliptin (as it is key for this thesis) were not considered. Some of this has been explored in previous studies.[82]

5.6 Context of this chapter in overall work

This study explored the T2DM cohort generated in Chapter 4 and also helped confirm that gliptins, mainly sitagliptin and sulphonylureas were the two most common treatments prescribed to individuals with T2DM as add-on to metformin in UK clinical practice. This importantly indicated that a comparative effectiveness study comparing sitagliptin against sulphonylureas as add-on to metformin would be feasible using THIN in terms of sample size available. In the next chapter, I will focus specifically on factors influencing the prescribing of these two treatments as add-on to

metformin. This chapter has also formed the basis of a published manuscript included in appendix for reference (Appendix H - Citation 1).

Chapter 6 Investigating patterns of prescribing for sitagliptin and sulphonylureas as add-on to metformin

6.1 Chapter Overview

Having confirmed that sitagliptin and sulphonylureas are the most common treatments added-on by physicians in UK primary care to metformin for type 2 diabetes mellitus (T2DM), I now aim to compare the characteristics of individuals prescribed sitagliptin to those prescribed sulphonylureas as add-on. This will help determine the factors which may be driving the decision to initiate both treatments respectively and is a key prerequisite in choosing confounding variables for inclusion in analysis in the cohort studies in Chapters 9 and 10.

6.2 Study background

In this chapter, I will determine the individual characteristics that differ among those initiated on sitagliptin as add-on compared to sulphonylureas. This will include an assessment of demographic characteristics, various health indicators including comorbidities and concomitantly prescribed treatments at the point of initiation of add-on treatment.

6.2.1 Study Objectives

1. To compare the demographic characteristics, comorbidities and concomitantly prescribed treatments of those prescribed sitagliptin against those prescribed sulphonylureas as add-on to metformin.
2. To highlight the key patient characteristics that determine clinician decisions to commence sitagliptin as opposed to sulphonylureas.

6.3 Methods

6.3.1 Cohort development

The generation of the T2DM cohort using The Health Improvement Network (THIN) database has been described earlier in Chapter 4 (Section 4.4). From this cohort, I then extracted individuals aged ≥ 18 years initiated on either sitagliptin or sulphonylureas as add-on to metformin between 2007 and 2014. The date an individual was first prescribed the add-on therapy was defined as the index date. This index date was used as the cut-off point to gather all baseline data for the cohort except where specified below. The inclusion and exclusion criteria are summarised more explicitly below.

Inclusion Criteria: Individuals aged 18-99 who were (i) permanently registered with a GP as defined by Patflag A and C (detailed in Chapter 4, Section 4.3.4) ii) had data that meets the required quality standards for THIN as determine by the ACU and AMR dates[91,92] (detailed in Chapter 4, Section 4.3.4) iii) have T2DM and were prescribed metformin with either sitagliptin or a sulphonylureas as add-on between 2007-2014* iv) have a minimum of 12 months of quality assured data prior to index date v) have a minimum of 6 months of quality assured data after the index date.

Scientific approval to undertake this study was obtained from CMD Medical Research's Scientific Review Committee in August 2016. (SRC Reference Number: 16-072).

*To confirm this was indeed add-on (and not a switch in anti-diabetic treatment), to be eligible for inclusion, individuals were required to have at least one prescription of metformin within 60 days after the index date.

Exclusion Criteria: Individuals prescribed any anti-diabetic other than metformin prior to the index date.

Variables of interest

Data was reported for all the variables listed below and the amount of missing data was also highlighted for each variable where relevant.

Demographic Variables: age at entry, year of entry, sex, ethnicity, Townsend Quintile.

General Health Indicators: HbA1c (haemoglobin A1c)*, weight**, Body Mass Index (BMI)**, systolic and diastolic blood pressure, total cholesterol, fasting plasma glucose, history of excessive alcohol intake, history of hypoglycaemias, face to face consultation frequency (mean number of face to face consultations per year).

*latest recorded value between 6 months before index date and up to 14 days after the index date

** latest recorded value between 12 months before index date and up to 14 days after the index date

Exposure related Variables: metformin dose, sulphonylurea type.

Comorbidities: cardiovascular disease, heart failure, anaemias, dementia, chronic kidney disease, liver disease, cancer, hypothyroidism, hyperthyroidism, arrythmia, neuropathy, retinopathy, pancreatitis.

Concomitant prescribed drugs†: anti-hypertensives, antiplatelets, anticoagulants, anti-heart failure, anti-arrythmic, diuretics, statins, other lipid lowering drugs, antidepressants,

antipsychotics, antiobesity, steroids (oral/intravenous), thyroxine, anti-thyroid drugs, anxiolytics and hypnotics.

†Concomitant means prescribed at least once in the 3 months prior to the index date

6.3.2 Statistical Analysis

Means and standard deviations were calculated for continuous variables except for those variables that were not normally distributed where medians and interquartile ranges were presented instead. Standardised differences with associated p-values were calculated for normally distributed continuous variables and also for dichotomous variables to facilitate comparison between the two treatment groups.[126] For all categorical variables, a chi squared test was used to test relative balance across sitagliptin and sulphonylurea groups.

For continuous variables the standardised mean difference (d) was defined as

d = (Mean of treatment - Mean of control)/ √[(SD of treatment)^2 + (SD of control)^2]/ 2 [126]

and for binary variables, the standardised difference (d) was defined as

d = (prevalence of treatment - prevalence of control)/ √[(prevalence of treatment (1 - prevalence of treatment) + (prevalence of control)(1 – prevalence of control)] / 2) [126]

Unlike t-tests and other statistical tests of hypothesis, the standardised difference is not influenced by sample size and also allows for comparison of relative balance across several covariates e.g. age and HbA1c at baseline.[126] However, the main limitation is there is no definitive agreement on what value for a standardised difference denotes a meaningful imbalance, though 0.1 (10%) is most commonly used in previous work and has been used here in my study as well.[126] Plots were created to visually examine trends over time in the distribution of several covariates such as weight and HbA1c among sitagliptin and sulphonylurea initiators commencing treatment in different calendar years as well as trends in comorbidities and concomitantly prescribed medications.

Logistic regression models were fitted with prescribing of sitagliptin or sulphonylureas as the binary outcome and covariates listed in Section 6.3.2 above as predictors. This analysis also facilitated creation of a kernel density plot to help visually identify the degree of overlap in the distribution of characteristics among sitagliptin and sulphonylureas initiators at the index date.

6.4 Results

6.4.1 Baseline Characteristics

A total of 4,630 individuals prescribed sitagliptin and 22,214 prescribed sulphonylureas as add-on to metformin were identified within the T2DM cohort described in Chapter 4 (Section 4.4). The characteristics of these individuals are summarised across Tables 6.1 to 6.3 and standardised differences have been reported where possible.

The mean age at index date was marginally lower in the sitagliptin cohort (58.8 years, standard deviation (SD) 11.6) compared to that for the sulphonylurea group (61.0 years, SD 12.1) (Table 6.1). However, sex, Townsend quintile and face to face consultation frequency showed similar distribution across both sitagliptin and sulphonylurea groups. In general, ethnicity was very poorly recorded with less than 40% of the individuals having a recorded ethnicity.

Table 6.1 Demographics of cohort at index date (baseline)

Demographics	Sita	Sulf	Stand Diff	P-value
Total, n	4,630	22,214		
Age(years), mean (SD)	58.8 (11.6)	61.0 (12.1)	-0.189	<0.001
Year of therapy initiation, n(%)				<0.001*
2007	33 (0.7)	2,374 (10.7)		
2008	140 (3.0)	3,214 (14.5)		
2009	467 (10.1)	3,711 (16.7)		
2010	975 (21.1)	3,387 (15.2)		
2011	855 (18.5)	2,979 (13.4)		
2012	937 (20.2)	2,735 (12.3)		
2013	801 (17.3)	2,550 (11.5)		
2014	422 (9.1)	1,264 (5.7)		
Sex, n(%)				
Male	2,769 (59.8)	13,632 (61.4)	-0.032	0.047
Female	1,861 (40.2)	8,582 (38.6)		
Missing, n(%)	0 (0)	0 (0)		
Ethnicity, n (%)				0.001*
White (Caucasian/Hispanic)	1,589 (34.3)	7,270 (32.7)		
Asian	11 (0.2)	46 (0.2)		
Black	116 (2.5)	844 (3.8)		
Mixed	53 (1.1)	254 (1.1)		
Other	31 (0.7)	158 (0.7)		
Unknown	2,830 (61.2)	13,642 (61.4)		
Townsend Quintile, n(%)				0.001*
1 (least deprived)	1,058 (22.9)	4,476 (20.1)		
2	901 (19.5)	4,488 (20.2)		
3	1,058 (22.9)	4,476 (20.1)		
4	902 (19.5)	4,463 (20.1)		
5 (most deprived)	672 (14.5)	3,387 (15.2)		
Missing, n(%)	159 (3.4)	719 (3.2)		

F2FC, mean (SD)	7.3 (5.3)	7.4 (5.1)	-0.018	0.245
Missing, n(%)	2 (0)	6 (0)		

*P-value derived from chi squared test.
Sita=Sitagliptin, Sulf=Sulphonylurea, SD=Standard Deviation, Stand Diff=standardised difference, F2FC=Mean Face to face consultation frequency per year.

A significant difference was observed between mean weight at baseline between the sitagliptin group (mean 99.5 kg, SD 22.1) and sulphonylurea group (mean 91.4 kg, SD 19.9) and also for mean HbA1c at baseline: sitagliptin (mean 71.3 mmol/mol, SD 15.5) and sulphonylureas (mean 75.6 mmol/mol, SD 19.5). However other important clinical measures such as smoking status and history of hypoglycaemias and excessive alcohol intake were well balanced (Table 6.2). Fasting Plasma Glucose at baseline was very poorly recorded.

Table 6.2 Clinical measures and exposure-specific information at index date (baseline)

General Health Indicators	Sita	Sulf	Stand Diff	P-value
Total, n	4,630	22,214		
Chronic Kidney Disease, n(%)				<0.001*
Creatinine Clearance > 60 ml/min	4,113 (88.8)	18,400 (82.8)		
Creatinine Clearance 30-59 ml/min	514 (11.1)	3,754 (16.9)		
Creatinine Clearance < 30 ml/min	3 (0.1)	60 (0.3)		
Smoking Status, n(%)				0.040*
Non-smoker	2,173 (46.9)	10,176 (45.8)		
Ex-smoker	1,411 (30.5)	6,617 (29.8)		
Current smoker	2,173 (46.9)	10,176 (45.8)		
Missing, n(%)	3 (0.1)	32 (0.1)		
SBP (mmHg), mean (SD)	133.7 (14)	134.3 (14.8)	-0.045	0.006
Missing	63 (1.4)	505 (2.3)		
DBP (mmHg), mean (SD)	79.1 (9.2)	78.5 (9.4)	0.072	<0.001
Missing, n(%)	63 (1.4)	505 (2.3)		
TC (mmol/l), mean (SD)	4.4 (1.1)	4.4 (1.2)	-0.050	0.003
Missing, n(%)	130 (2.8)	808 (3.6)		
Body weight(kg), mean (SD)	99.5 (22.1)	91.4 (19.9)	0.385	<0.001
Missing, n(%)	182 (3.9)	1,271 (5.7)		
BMI (kg/m2), mean (SD)	34.3 (6.6)	31.8 (6.1)	0.396	<0.001
Missing, n(%)	219 (4.7)	1,447 (6.5)		
HbA1c (mmol/mol), mean (SD)	71.3 (15.5)	75.6 (19.5)	-0.242	<0.001
Missing, n(%)	130 (2.7)	869 (3.9)		
HbA1c distribution at baseline, n(%)				<0.001*
HbA1c<64 mmol/mol	1,649 (35.6)	6,569 (29.6)		
HbA1c ≥64 to <75 mmol/mol	1,417 (30.6)	6,116 (27.5)		
HbA1c ≥ 75 mmol/mol	1,440 (31.1)	8,668 (39)		
HbA1c (%), mean (SD)	8.7 (1.4)	9.1 (1.8)	-0.242	<0.001
Missing, n(%)	130 (2.7)	869 (3.9)		
FPG (mmol/l)	10.6 (3.5)	11.5 (4.8)	-0.216	<0.001
Missing, n(%)	3,640 (78.6)	17,610 (79.3)		
History of excessive alcohol intake, n(%)**	686 (14.8)	3,154 (14.2)	-0.018	0.274
History of hypoglycaemias, n(%)	25 (0.5)	181 (0.8)	0.034	0.051
Exposure related variables				
Metformin dose ≥1500mg/day, n(%)	3,591 (77.6)	16,855 (75.9)	-0.040	0.014
Metformin dose <1500mg/day, n(%)	1,039 (22.4)	5,359 (24.1)		
Sulphonylurea Type, n(%)				
Gliclazide	-	20,469 (92.1)		
Glipizide	-	629 (2.8)		
Glibenclamide	-	130 (0.6)		
Tolbutamide	-	103 (0.5)		
Glimepiride	-	1,612 (7.3)		
Chlorpropamide	-	0 (0)		
Other	-	1 (0)		

*P-value derived from chi squared test.
**Defined as recording of an intake of >35 units of alcohol a week for males or > 28 units for females.
Sita=Sitagliptin; Sulf=Sulphonylurea, SD=Standard Deviation, Stand Diff=standardised difference,

SBP=Systolic Blood Pressure, DBP= Diastolic Blood pressure, TC= Total Cholesterol, BMI= Body Mass Index, FPG= Fasting Plasma Glucose.

Individuals initiated on sitagliptin had in general less comorbidities than those on sulphonylureas except in the case of history of retinopathy as shown in Table 6.3 (16.1% for sitaliptin vs 13.4% for sulphonylureas). In particular, a lower prevalence of cardiovascular disease (25.5% vs 29.4%), heart failure (10.5% vs 11.7 %) and cancer (13.3% vs 14.3%) was observed for sitagliptin vs sulphonylureas respectively. Fewer individuals prescribed sitagliptin had an anti-platelet (31.2% vs 38.0 %), or oral/intravenous steroids (3.8% vs 5.6%) prescribed within the 3 months before the index date (Table 6.3), while more individuals prescribed sitagliptin had antiobesity drugs (2.4% vs 1.2%) and statins prescribed (78.4% vs 76.5%).

Table 6.3 Comorbidities and concomitantly prescribed medication at index date (baseline)

Comorbidities and concomitantly prescribed treatment	Sita	Sulf	Stand Diff	P-value
Total, n	4,630	22,214		
Comorbidities, n(%)				
Cardiovascular disease	1,181 (25.5)	6,533 (29.4)	0.088	<0.001
Heart failure	486 (10.5)	2,601 (11.7)	0.039	0.019
Anaemias	405 (8.7)	1,927 (8.7)	-0.003	0.873
Dementia	32 (0.7)	164 (0.7)	0.006	0.732
Liver disease	168 (3.6)	810 (3.6)	0.001	0.953
Cancer	614 (13.3)	3,182 (14.3)	0.031	0.059
Hypothyroidism	373 (8.1)	1,822 (8.2)	0.005	0.742
Hyperthyroidism	53 (1.1)	315 (1.4)	0.024	0.146
Arrythmia	312 (6.7)	1,703 (7.7)	0.036	0.029
Pancreatitis	49 (1.1)	333 (1.5)	0.039	0.021
Neuropathy	157 (3.4)	894 (4.0)	0.034	0.043
Retinopathy	747 (16.1)	2,980 (13.4)	-0.077	<0.001
Concomitant prescribing, n(%)*				
Anti-hypertensive	3,188 (68.9)	15,243 (68.6)	-0.005	0.752
Antiplatelets	1,443 (31.2)	8,439 (38.0)	0.144	<0.001
Anticoagulants	204 (4.4)	992 (4.5)	0.003	0.858
Anti-arrythmic	22 (0.5)	150 (0.7)	0.026	0.121
Diuretics	1,185 (25.6)	5,954 (26.8)	0.027	0.090
Statins	3,628 (78.4)	16,997 (76.5)	-0.044	0.007
Other lipid lowering drugs	254 (5.5)	1,134 (5.1)	-0.017	0.287
Antidepressants	850 (18.4)	3,921 (17.7)	-0.018	0.252
Antipsychotics	88 (1.9)	489 (2.2)	0.021	0.199
Antiobesity	111 (2.4)	275 (1.2)	-0.087	<0.001
Steroids –oral/iv	177 (3.8)	1,252 (5.6)	0.085	<0.001
Thyroxine	360 (7.8)	1,808 (8.1)	0.013	0.409
Anti-thyroid drugs	4 (0.1)	29 (0.1)	0.013	0.435
Anxiolytics and Hypnotics	212 (4.6)	1,261 (5.7)	0.050	0.003

*Prescribed within 3 months prior to index date. Sita=Sitagliptin, Sulf=Sulphonylurea, stand diff=standardised difference, iv=intravenous.

6.4.2 Distribution of HbA1c and weight at the index date (baseline)

In Figure 6.1, I present histograms of the distribution of HbA1c among sitagliptin and sulphonylurea initiators. In Figure 6.2, I present similar histograms for weight. In both instances, the histograms show that distribution of HbA1c and weight across both groups are highly similar at baseline.

In Chapter 9, I will present a cohort study examining change in HbA1c and weight from baseline among those initiated on sitagliptin compared to those initiated on a sulphonylurea. Hence, the distribution of HbA1c and weight at baseline is of particular importance here.

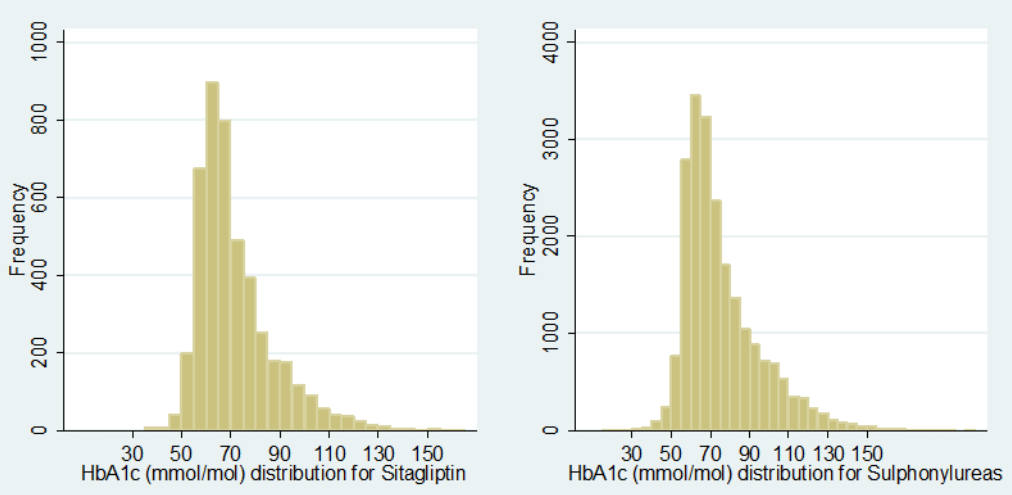


Figure 6.1 Distributions of HbA1c (mmol/mol) at index date (point of initiation of prescribing) of sitagliptin (left) and sulphonylureas (right)

6.4.3 Missing Data

The amount of missing data across all covariates at baseline was similar between the sitagliptin and sulphonylurea groups (Tables 6.1 to 6.3). The level of missing data was highest for fasting plasma glucose (78.6% missing for sitagliptin and 79.3% missing for sulphonylurea users) and for ethnicity with over 60% of individuals prescribed sitagliptin and sulphonylureas having no recorded ethnicity.

When these two variables (fasting glucose and ethnicity) were excluded, there were 23,035 individuals out of 26,844 identified with complete data for all remaining covariates outlined in Tables 6.1 to 6.3. This consisted of 4,074 individuals prescribed sitagliptin and 18,961 prescribed sulphonylureas.

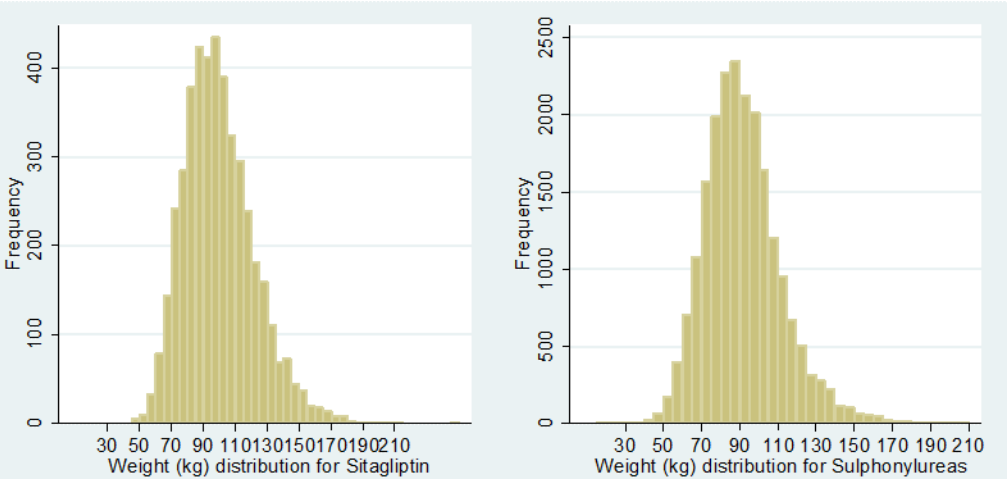


Figure 6.2 Distributions of weight (kg) at index date (point of initiation of prescribing) of sitagliptin (left) and sulphonylureas (right)

6.4.4 Temporal changes in covariates at baseline

Changes in means and medians of several key clinical measures such as weight and HbA1c as well as comorbidities and concomitant prescriptions at baseline were examined between 2007 and 2014. Changes observed affected both sitagliptin and sulphonylurea groups equally. Graphs depicting these time trends are included in Appendix D for reference (Supplementary Figures 6A1-6A3).

6.4.5 Propensity for sitagliptin prescribing

The propensity for being prescribed sitagliptin based on the 23,035 cases with complete data for the covariates listed in Tables 6.1 to 6.3 (excluding ethnicity and fasting plasma glucose) is displayed in Figure 6.3. The overlap between the two curves highlights the individuals with complete data that had an equal propensity to be prescribed a sitagliptin and sulphonylureas. This graph will be revisited in Chapter 9 prior to completing the propensity score matching analysis.

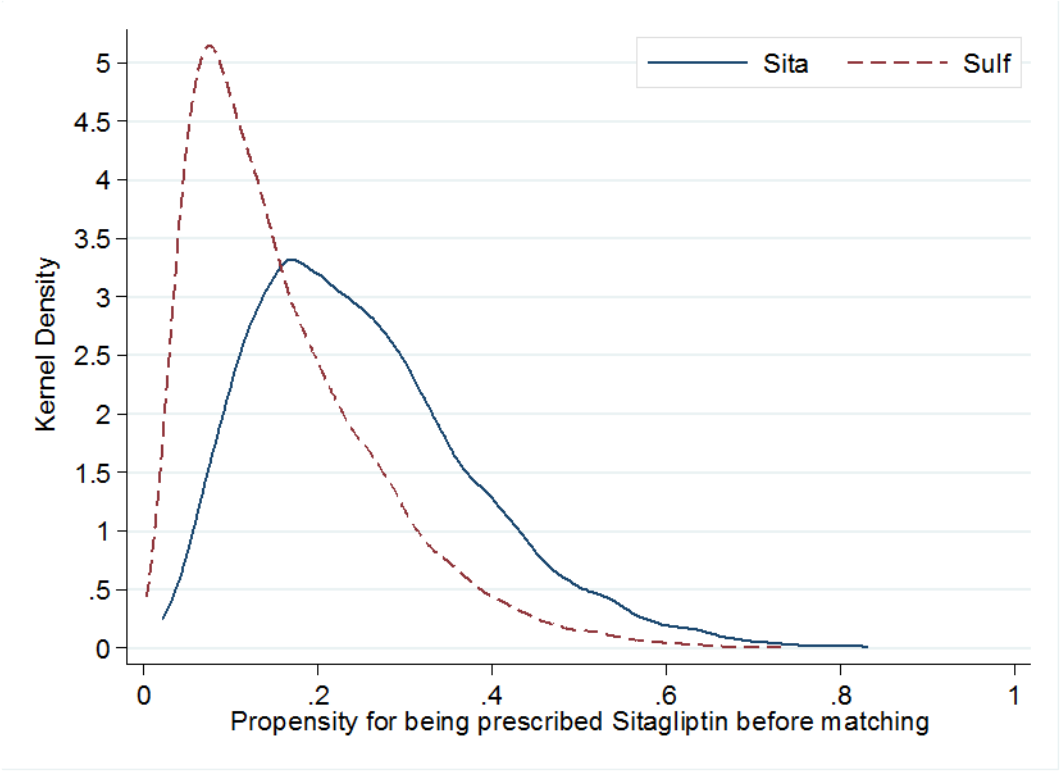


Figure 6.3 Kernel density plot of propensity for being prescribed sitagliptin based on distribution of measured characteristics at baseline for both individuals prescribed sitagliptin and sulphonylureas

*This plot is a predictive plot of prescribing sitagliptin based on a logistic regression with sitagliptin treatment as the outcome. Details of the full regression analysis and output can be found in the Appendix D (Supplementary Figure 6A4).

6.5 Discussion

6.5.1 Summary of main findings

The main purpose of this descriptive study was to identify and highlight the factors which differed most substantially between individuals that had sitagliptin added-on to metformin as opposed to sulphonylureas. Individuals prescribed sitagliptin were in general heavier in weight and had a lower HbA1c recorded at the index date. Individuals prescribed sitagliptin had less comorbidities, particularly with respect to cardiovascular and related cardiac diseases, which was naturally reflected in the concomitantly prescribed medications. Temporal changes examined across covariates did not highlight increasing disparity emerging between individuals commenced on either sitagliptin or sulphonylureas over time. The kernel density plot revealed that there was some overlap in the distribution of covariates across sitagliptin and sulphonylurea initiators. This indicated that there were individuals across the sitagliptin and sulphonylurea groups that shared similar characteristics at the index date. I will investigate this finding further in Chapter 8.

6.5.2 Comparison with existing literature

Guidance from the National Institute for Health and Care Excellence first made reference to the use of sitagliptin and the class of gliptins as a whole in the 2009 guidance.[16] It was recommended that sitagliptin be used as add-on to metformin when "*blood glucose control becomes inadequate or if: the person is at significant risk of hypoglycaemia or its consequences or the person does not tolerate or is contraindicated to a sulphonylurea.*" [16] I therefore expected to find a higher prevalence of hypoglycaemia among sitagliptin users at baseline than sulphonylurea users. Though this was found to be the case, the overall proportion of individuals recorded with a history of hypoglycaemia was very low (0.5% in sitagliptin users and 0.8% among sulphonylurea initiators). This was even after a search for terms relevant to hypoglycaemia was conducted in the freetext in THIN. On the one hand, coding for hypoglycaemia in databases has been shown in previous studies to be quite poor which might explain low prevalence.[127] However, also worth considering is that individuals selected in this study were required to have only been prescribed metformin (no other anti-diabetic medication) and metformin alone has a very low risk of inducing hypoglycaemia.[128] Hence, this could also explain the low prevalence of hypoglycaemia. As a result, it remains unclear whether cases of hypoglycaemia may have been missed due to lack of recording or, whether in fact, the history of hypoglycaemias among these individuals was indeed this low.

NICE guidelines previous to the most recent 2015 update, suggested that sitagliptin be reserved for those who are potentially more difficult to manage. Hence, it was interesting to find that the sulphonylurea users had, in general, more comorbidities. This may be due to physicians choosing to use conventional and more familiar treatments for more difficult to manage individuals as has been evidenced in previous chronic disease research.[129]

Prevalence of cardiovascular disease, heart failure and other cardiovascular disorders were all higher among the sulphonylurea groups. This may be related to initial uncertainty about the cardiovascular safety of gliptins as a class when they were first licensed, leading to reluctance among some prescribers to initiate them in individuals with a significant cardiac history. In 2013, a signal was raised regarding gliptins as a class following the secondary analysis of a trial conducted on saxagliptin which suggested it may have a risk of exacerbating heart failure.[130] However, this hypothesized cardiovascular risk has been largely allayed following recent cardiovascular trial data for sitagliptin published in 2015. [28,44] A small increased risk of pancreatitis with sitagliptin has been signalled and included in the product label, hence it was unsurprising to

find a slightly lower history of pancreatitis among initiators of sitagliptin than sulphonylureas (1.1% vs 1.5%). Prevalence of cancer at time of add-on treatment initiation was also higher among the sulphonylurea initiators. A signal for an increased risk of pancreatic cancer with sitagliptin was previously observed which may have led prescribers to favour the use of sulphonylureas in some individuals with cancer.[131-133] However this signal too has been allayed in recent studies.[44,134]

The most recent 2015 NICE T2DM guidance closely matches those from the European Association for Study of Diabetes and American Diabetes Association where far more liberal recommendations have been made about add-on treatments to metformin.[22,24] Sitagliptin is now recommended by NICE as a monotherapy alternative to metformin and still remains as one of the possible options for add-on to metformin alongside sulphonylureas.[22]

6.6 Context of this chapter in overall work

This chapter helps inform on which covariates, measured at baseline, have the most impact on a clinician deciding between commencing sitagliptin or sulphonylureas as add-on to metformin, and also how these factors have changed over time. This will be key when finalising the confounding variables to account for in the analysis of my cohort studies in Chapters 9 and 10. The next chapter will involve exploring the distribution of the main outcomes of interest and their relationship with the potential confounding covariates.

Chapter 7 Investigating recording of the outcomes

7.1 Chapter Overview

In this chapter, I will determine the feasibility of using data from THIN (The Health Improvement Network) to investigate four outcomes for individuals with T2DM (type 2 diabetes mellitus) prescribed sitagliptin or sulphonylureas as add-on to metformin. These outcomes include: 1) change in HbA1c (haemoglobin A1c) approximately 12 months after initiation of add-on treatment: 2) change in weight approximately 12 months after initiation of add-on treatment: 3) time to first recording of a HbA1c > 58 mmol/mol and 4) time to first recording of an anti-diabetic treatment regimen change. The studies examining the first two outcomes will be presented in Chapter 9, while the studies for the latter two outcomes will be presented in Chapter 10.

7.2 Study background

A HbA1c test, as described in Chapter 1 (Section 1.3), is a blood test that provides a value reflective of glycaemic control for past 2-3 months for an individual and is the most common method used for monitoring glycaemic control for individuals with T2DM once they have commenced on medication.[22] Maintaining optimal glycaemic control has been shown in many studies to lead to a reduction in rates of macrovascular and microvascular complications of T2DM.[8] The National Institute for Health and Care Excellence (NICE) have recommendations for HbA1c targets for individuals though they state that these may need to be individualised based on tolerance to therapy and specific factors such as age and comorbidities. However, the general recommendation that applies to most individuals once on a single treatment such as metformin is to aim for a HbA1c of 48 mmol/mol (6.5%) or a higher target of 53 mmol/mol (7.0%) if there is a particular concern regarding hypoglycaemia.[22] If this is not achieved despite lifestyle alterations and medication adherence, the clinician is advised to consider treatment intensification particularly if the HbA1c has become > 58 mmol/mol (7.5%).[16,22] This part of the guidance regarding HbA1c targets has not changed over time despite the various NICE updates. NICE also recommend that HbA1c is measured at 3–6-monthly intervals until it is stable after commencement of a new therapy and at 6-monthly intervals once the person has been stabilised on treatment in terms of their HbA1c levels.[22]

Being overweight is strongly correlated with the onset of T2DM and worsening of the disease.[22,135,136] Targets for weight control vary depending on age, height, ethnicity as well as comorbidities and should be agreed together with the individual. [135,136] NICE guidance does not

recommend a specific frequency for monitoring weight and in fact suggests self-monitoring is often the best option to keep the individual motivated.[137] However, they do recommend that clinicians set an initial body weight loss target of 5–10% for individuals with newly diagnosed T2DM who are overweight or obese.[22]

My third outcome of interest will involve examining the time before individuals have a recording of a HbA1c >58 mmol/mol. Guidance from NICE states that recording of a HbA1c > 58 mmol/mol is indicative of poor glycaemic control.[22] Though targets may need to be individualised in certain cases, this cut off is applicable to most individuals.[22] This is because two landmark trials: one for type 1 diabetes mellitus, the Diabetes Control and Complications Trial (DCCT),[138] and another for T2DM, UK Prospective Diabetes Study (UKPDS),[121] have both convincingly demonstrated that intensive glycaemic control below 58 mmol/mol (7.5%) reduces rates of microvascular and macrovascular complications of diabetes. Thus, this date of recording of a HbA1c >58 mmol/mol is of importance as it represents the date on which the individual has failed to maintain this desirable glycaemic target.

The fourth and final outcome I will examine is the time before the clinician decides that a change in anti-diabetic therapy is required to manage an individual's T2DM. This is through issue of a prescription of an anti-diabetic other than metformin or the initial add-on treatment (i.e. sitagliptin or sulphonylurea).[22,41] This treatment change is most commonly due to inadequate glycaemic control, however can also occur due to poor adherence, intolerance to therapy or simply individual patient preference. NICE guidance recommends that treatment change should be strongly considered when the HbA1c exceeds 58 mmol/mol for most individuals. However, despite this guidance, clinical inertia in individuals with T2DM has been identified as a well-established problem.[74] Studies have found that individuals sometimes remain in suboptimal glycaemic control for large periods of time before treatment is changed.[74,139,140]

In summary, maintaining HbA1c and weight within targets appropriate to that individual is a cornerstone of management for individuals with T2DM. Thus, these are both useful markers for measuring the "real world" effectiveness of T2DM treatments. Another important measure of treatment effectiveness is an analysis of when the first undesirable HbA1c > 58 mmol/mol is recorded after initiation of add-on or equally, when an anti-diabetic treatment regimen change is first made. Thus collectively these four outcomes will provide useful insight into "real world" effectiveness of sitagliptin compared to sulphonylureas in clinical practice.

In this chapter, in order to ascertain the feasibility of designing studies to explore these four outcomes detailed above, I will complete the objectives listed below.

7.2.1 Study Objectives

Among those initiated on sitagliptin vs sulphonylureas as add-on to metformin, I will:

1. Compare the length of follow-up time available for individuals from the index date on which initiation of sitagliptin or sulphonylureas add-on took place
2. Compare the frequency of recording of HbA1c over time
3. Compare the frequency of recording of weight over time

Among those initiated on sitagliptin or sulphonylureas as add-on to metformin, I will:

4. Examine the frequency of recording of first HbA1c > 58 mmol/mol over time
5. Examine the frequency of change in anti-diabetic treatment (through prescribing of an anti-diabetic other than metformin and sitagliptin or sulphonylureas respectively) over time
6. Examine the relationship between (i) change in HbA1c from baseline, (ii) change in weight from baseline, (iii) recording of first HbA1c > 58 mmol/mol and (iv) recording of first change in anti-diabetic treatment with covariates related to demographics, comorbidities and prescribed medications
7. Identify those characteristics that most influence (i) change in HbA1c, (ii) change in weight, (iii) recording of first HbA1c > 58 mmol/mol and (iv) recording of first change in anti-diabetic treatment

7.3 Methods

7.3.1 Cohort development

The development of the sitagliptin and sulphonylurea cohorts and details of all covariates of interest have been described already in detail in Chapters 4 (Section 4.3.6) and 6 (Section 6.3.1). Scientific approval to undertake this study was obtained from CMD Medical Research's Scientific Review Committee in August 2016. (SRC Reference Number: 16-072).

7.3.2 Statistical Analysis

Frequencies and means of HbA1c and weight recordings were examined starting from the index date (more precisely index date + 14 days to ensure the value had not already been included as part of the baseline measurements) on which sitagliptin or a sulphonylureas was initiated for a follow-up period of 30 months (2.5 years). This was first explored by determining the percentage

of individuals with recordings of HbA1c and weight in each 3 month interval after the index date and subsequently in each 6 and then 9 monthly intervals. I will present the findings for 3 and 9 monthly intervals in the main chapter as these are most pertinent [6 monthly analysis will be included in Appendix E (Supplementary Figure 7A1) for reference]. The number of recordings of a HbA1c >58 mmol/mol and recording of a change in treatment across the entire cohort (sitagliptin and sulphonylurea initiators) was also determined for this 30 month period after the index date. These frequencies for recording were then plotted graphically against time.

I then explored the relationship of the covariates (demographic, comorbidities etc.) with all four outcomes of interest.

For the first two outcomes examining HbA1c and weight, I used the earliest recording between 9-18 months after index date as the value for final HbA1c and weight. This was in order to retrieve a recorded value as close to 12 months after initiation, minimise the impact of missing data and to allow a sufficient period for the add-on treatment to have an effect. Using this final HbA1c or final weight as the outcome, I first undertook a simple linear regression analysis with each covariate (detailed in Chapter 6, Section 6.3.1) in turn. For HbA1c and weight, as I was interested in examining change, a regression analysis was also conducted with each covariate in turn with adjustments for the baseline value for HbA1c or weight respectively. Another third regression analysis was conducted including sex and age at entry in the model as well. Finally, those covariates identified as being strongly associated with HbA1c and weight from this third model ($p<0.1$), were then included in a multivariable regression model to determine values of coefficients for the different covariates after adjustment. I then undertook a stepwise regression, where I removed variables with the highest p-value (as long as it was > 0.1) in the multivariable model. I also undertook a likelihood ratio test to determine if this produced a better fitted model at each stage. This was undertaken until a final parsimonious multivariable model was obtained where all variables were significant at the ($p<0.1$) threshold.

I then examined the relationship between the covariates and the last two outcomes: time before first recording of a HbA1c > 58 mmol/mol and time before first recording of a change in anti-diabetic treatment. For this analysis, I used a longer follow-up of 30 months (2.5 years) after the index date. This period was chosen because the vast majority of first recordings of a HbA1c > 58 mmol/mol occurred during this follow-up time and the cohort size diminished considerably thereafter. I also required a minimum of 3 months period to lapse after initiation of the add-on treatment, before considering HbA1c recordings to give time for the respective treatments to have

effect. This regression analyses was undertaken in a similar stepwise manner to my analysis for HbA1c and weight described above except with use of a Cox regression model to account for the fact that I was undertaking a survival analysis with a binary outcome.[141]

7.4 Results

7.4.1 Length of individual follow-up

Of a total of 4,630 individuals initiated on sitagliptin between 2007 and 2014, 4,080 (88.1%) were followed up for at least 1 year, 3,215 (67.5%) for at least 2 years and 1,326 (28.6%) had more than 4 years follow-up as illustrated in Figure 7.1. Of the 22,214 initiated on sulphonylureas, 20,103 (90.5%) had at least 1 year follow-up, 16,289 (73.3%) had at least 2 years and 9,670 (43.5%) had more than 4 years of follow-up.

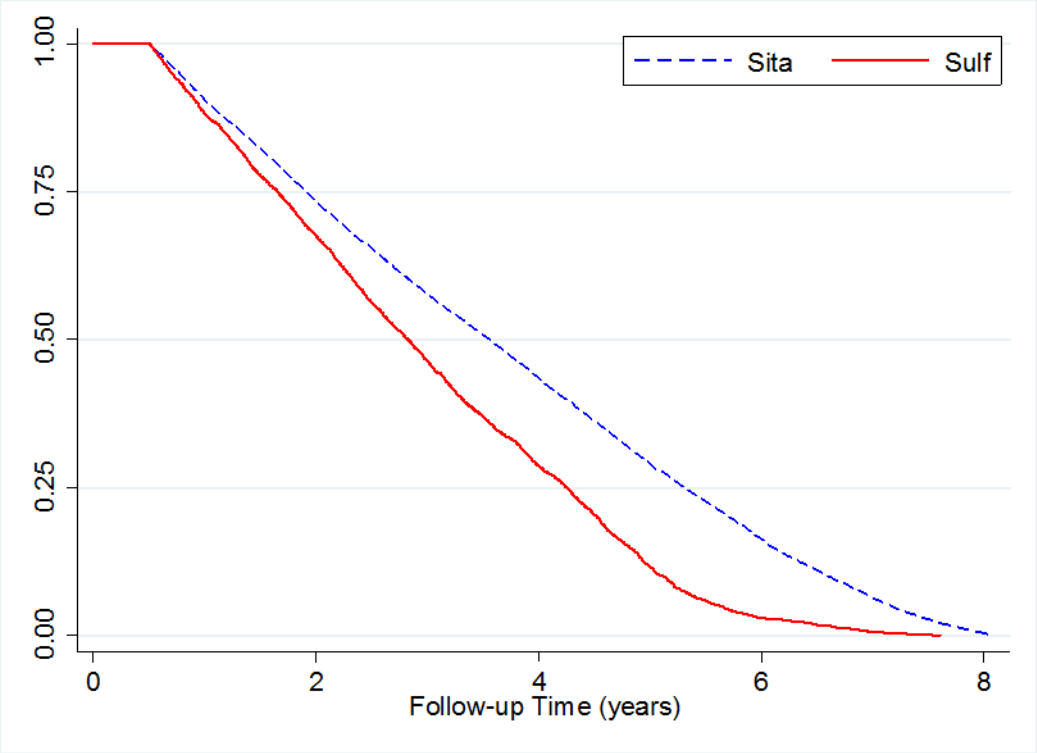


Figure 7.1 Proportion reaching specified follow-up times (years) after index date for initiation of add-on treatment
Note: Initial plateau is due to requirement that entry into cohort required an individual to have at least 0.5 years (6 months) of data after index date.

7.4.2 Temporal change in number of recordings of HbA1c, weight, HbA1c > 58 mmol/mol and treatment regimen change after index date

7.4.2.1 Recording of HbA1c

The number of individuals with a HbA1c recording as a percentage of those who still had an active record (registered with THIN affiliated practice and not left the practice or died) at the successive

time points decreased over time (Figure 7.2). Additionally, the number remaining at each time point after add-on initiation as a percentage of the original cohort is also detailed in Table 7.1. Importantly, the percentage decreased similarly over time in both sulphonylurea and sitagliptin groups.

Of those individuals with an active record 12 months after the index date, 1708 (41.9%) of 4,080 individuals initiated on sitagliptin and 8709 (43.3%) of 20,103 individuals initiated on sulphonylureas had a HbA1c value recorded between 12 and 15 months after the index date (Figure 7.2). However, 3,613 (82.9%) of 4,356 individuals initiated on sitagliptin and 17,742 (83.7%) of 21,191 on sulphonylureas had an HbA1c value recorded in the larger 9 month interval, 9 to 18 months after the index date (Table 7.2).

7.4.2.2 Recording of Weight

The number of individuals with a weight recording as a percentage of those who still had an active record at the successive time points also decreased similarly over time in both sulphonylureas and sitagliptin groups (Figure 7.2). Of those individuals with an active record 12 months after the index date, 1,614 (39.6%) of 4,080 individuals on sitagliptin and 7,642 (38.0%) of 20,103 on sulphonylureas had a weight recorded 12 to 15 months after the index date (Table 7.1). However 3,315 (76.1%) of 4,356 on sitagliptin and 15,924 (75.1%) of 21,191 on sulphonylureas had a weight recording between 9 and 18 months after the index date (Table 7.2).

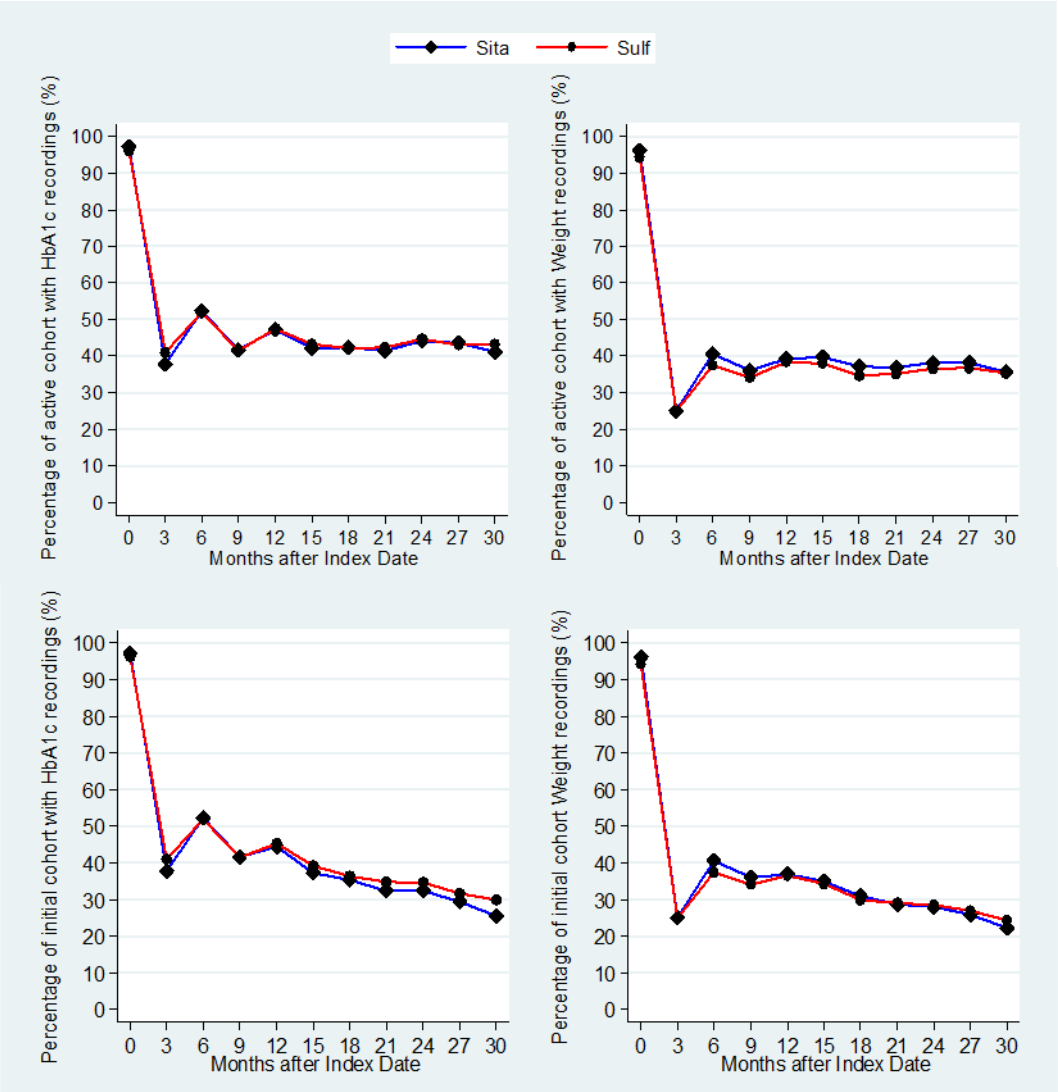


Figure 7.2 Percentage of individuals with HbA1c and weight recordings over time (3 monthly intervals) of those that are active in each respective 3 monthly period (top graphs) and of initial cohort (bottom two graphs)

*active refers to those patients that are still registered in THIN database at that point (i.e. not left practice or died)

Table 7.1 Percentage of individuals with HbA1c and weight recordings over time (3 monthly intervals) in each respective 3 monthly period

Month	Baseline		0.5-3		3-6		6-9		9-12		12-15		15-18		18-21		21-24		24-27		27-30	
	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf
Number of individuals with a HbA1c record as a percentage of those active* at beginning of period, n (%)	4,506 (97.3)	21,353 (96.1)	1,742 (37.6)	9,119 (41.1)	2,423 (52.3)	11,542 (52.0)	1,919 (41.4)	9,207 (41.4)	2,060 (47.3)	10079 (47.6)	1,708 (41.9)	8,709 (43.3)	1,634 (42.3)	8,088 (42.2)	1,479 (41.1)	7,758 (42.4)	1,500 (44.4)	7,717 (44.6)	1,351 (43.2)	7,028 (43.1)	1,177 (41.0)	6,648 (43.2)
Percentage of initial cohort with HbA1c record, (%)	97.3	96.1	37.6	41.1	52.3	52.0	41.4	41.4	44.5	45.4	36.9	39.2	35.3	36.4	31.9	34.9	32.4	34.7	29.2	31.6	25.4	29.9
Number of individuals with a weight record as a percentage of those active* at beginning of period, n (%)	4,448 (96.1)	20,943 (94.3)	1,161 (25.1)	5,521 (24.9)	1,879 (40.6)	8,301 (37.4)	1,657 (35.8)	7,593 (34.2)	1,707 (39.2)	8,119 (38.3)	1,614 (39.6)	7,642 (38.0)	1,436 (37.2)	6,643 (34.6)	1,321 (36.7)	6,451 (35.3)	1,294 (38.3)	6,341 (36.6)	1,188 (38.0)	5,980 (36.7)	1,023 (35.6)	5,424 (35.3)
Percentage of initial cohort with weight record, (%)	96.1	94.3	25.1	24.9	40.6	37.4	35.8	34.2	36.9	36.5	34.9	34.4	31.0	29.9	28.5	29.0	27.9	28.5	25.7	26.9	22.1	24.4
Individuals with active records remaining at beginning of period	4,630	22,214	4,630	22,214	4,630	22,214	4,630	22,214	4,356	21191	4,080	20,103	3,864	19,180	3,602	18,278	3,379	17,308	3,125	16,289	2,870	15,375

*active refers to those individuals that are still registered in THIN database at that point (i.e. not left practice, died)

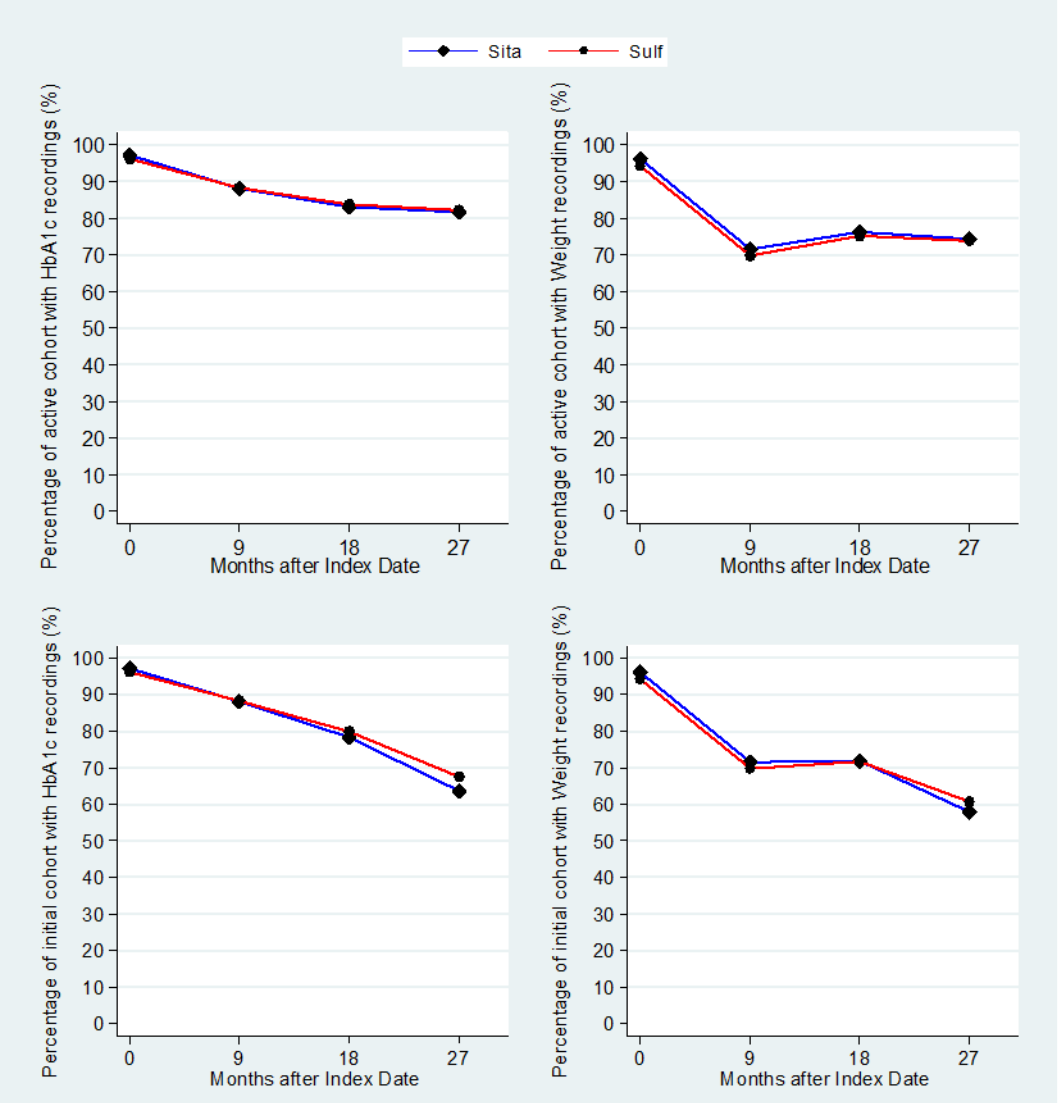


Figure 7.3 Percentage of individuals with HbA1c and weight recordings over time (9 monthly intervals) of those that are active in each respective 9 monthly period (top graphs) and of initial cohort (bottom two graphs)

*active refers to those patients that are still registered in THIN database at that point (i.e. not left practice or died)

Table 7.2 Percentage of individuals with HbA1c and weight recordings over time (9 monthly intervals) in each respective 9 monthly period

Month	**Baseline**		**0.5-9**		**9-18**		**18-27**	
	Sita	Sulf	Sita	Sulf	Sita	Sulf	Sita	Sulf
Number of individuals with a HbA1c record as a percentage of those active* at beginning of period, n (%)	4,506 (97.3)	21,353 (96.1)	4,081 (88.1)	19,635 (88.4)	3,613 (82.9)	17,742 (83.7)	2,934 (81.5)	15,022 (82.2)
Percentage of initial cohort with HbA1c record, (%)	86.7	88.4	78.5	81.3	69.5	73.5	56.4	62.2
Number of individuals with a weight record as a percentage of those active* at beginning of period, n (%)	4,448 (96.1)	20,943 (94.3)	3,309 (71.5)	15,512 (69.8)	3,315 (76.1)	15,924 (75.1)	2,672 (74.2)	13,487 (73.8)
Percentage of initial cohort with weight record, (%)	85.6	86.7	63.6	64.2	63.8	65.9	51.4	55.8
Individuals with active records remaining at beginning of period	4,630	22,214	4,630	22,214	4,356	21,191	3,602	18,278

*active refers to those individuals that are still registered in THIN database at that point (i.e. not left practice or died)

7.4.2.3 Number of individuals with a recording of a HbA1c > 58 mmol/mol

The proportion of individuals with no recording of a HbA1c > 58 mmol/mol during follow-up is displayed in Figure 7.4A. In total, 18,477 individuals (68.8%) from an eligible cohort of 26,844 individuals had a HbA1c > 58 mmol/mol recorded (Table 7.3). 16,419 (88.9%) of these 18,477 individuals recorded this HbA1c > 58 mmol/mol within 30 months (2.5 years) after the index date.

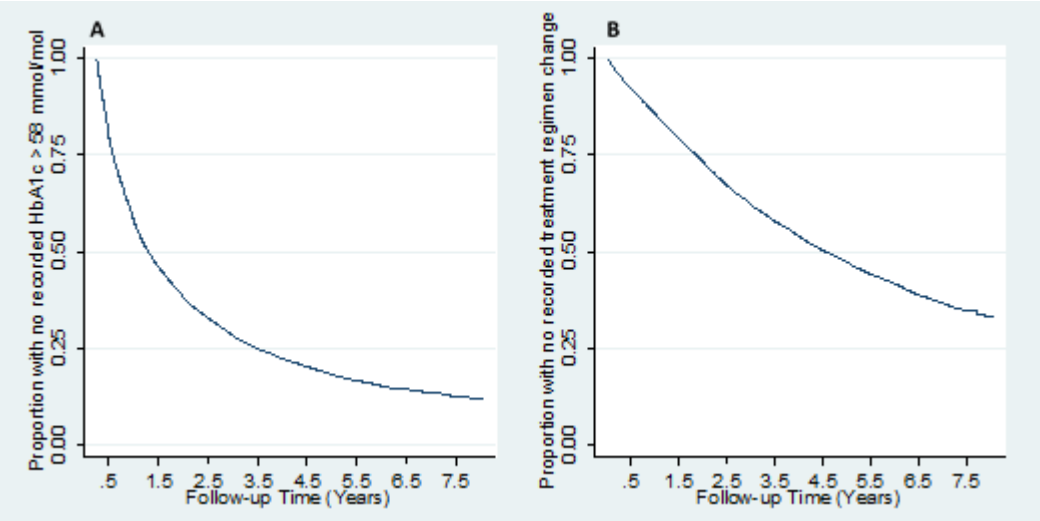


Figure 7.4 Proportion of individuals with no recorded HbA1c > 58 mmol/mol (A) and no recorded treatment regimen change (B) during follow-up.

7.4.2.4 Number of individuals with a recording of treatment regimen change

The proportion of individuals with no recording of a treatment regimen change during follow-up is displayed in Figure 7.4B. In total, 10,467 individuals (39.0%) from an eligible cohort of 26,844 individuals had an anti-diabetic treatment regimen change recorded (Table 7.4). 7,597 (72.6%) of these 10,467 individuals recorded this treatment change within 30 months (2.5 years) after the index date.

Table 7.3 Number of individuals with a record of a HbA1c >58 mmol/mol over time

Years	Baseline	0.25-1.5	1.5-2.5	2.5-3.5	3.5-4.5	>4.5	Total
No. of individuals with a recording of HbA1c > 58mmol/mol before end of period	NA	13,827	2,592	1,185	507	366	**18,477**
No. of individuals with no recording of HbA1c > 58mmol/mol within period or subsequently		8,367	5,356	3,545	2,378	1,462	**N/A**
No. of individuals with no recording of HbA1c > 58mmol/mol within period including those that have a recording subsequently		10,006	5,603	3,251	1,828	0	**NA**
No. of individuals leaving the practice before end of period without a recording of HbA1c > 58mmol/mol (Not including deaths)		2,597	1,529	952	690	1,204	**6,972**
No. of individuals dying within each period		414	282	215	226	258	**1,395**
No. of individuals in cohort at beginning of each period (individuals at risk)		26,844	10,006	5,603	3,251	1,828	

No=Number

Table 7.4 Number of individuals with a record of a treatment regimen change over time

Years	Baseline	0-1.5	1.5-2.5	2.5-3.5	3.5-4.5	>4.5	Total
No. of individuals with a recording of treatment change	NA	5,253	2,344	1,381	820	669	**10,467**
No. of individuals with no recording of a treatment change within period or subsequently		16,377	12,156	8,586	5,967	3,769	**NA**
No. of individuals with no recording of a treatment change within period including those that have a recording subsequently		17,370	11,456	7,456	4,438	0	**NA**
No. of individuals leaving the practice before end of period without recording of treatment change (Not including deaths)		3,807	3,288	2,404	1,972	3,511	**14,982**
No. of individuals dying within each period		414	282	215	226	258	**1,395**
No. of individuals in cohort at beginning of each period (individuals at risk)		26,844	17,370	11,456	7,456	4,438	

No=Number

7.4.3 Relationship between covariates and each outcome

7.4.3.1 Change in HbA1c from baseline

The results of the regression analyses with the final HbA1c being used as the outcome are shown in Table 7.5 below. The final HbA1c used was the earliest recorded HbA1c for each individual between 9-18 months after the index date. In total, 21,355 individuals [3,613 (82.9%) of all individuals prescribed sitagliptin and 17,742 (83.7%) of all prescribed sulphonylureas] had a baseline HbA1c and final HbA1c value recorded.

A positive association between the baseline HbA1c and the final recorded HbA1c was found to exist: 0.28 mmol/mol (95% Confidence Interval 0.27 to 0.29) in the multivariable analysis. This indicated that for every 1 mmol/mol unit increase in baseline HbA1c, a 0.28 mmol/mol increase was observed in the final recorded HbA1c, after adjusting for other significant variables. A similar positive association was also observed with being female compared to male: 1.62 mmol/mol (95% CI 1.16 to 2.08). This indicated that females had a 1.62 mmol/mol higher final HbA1c on average after adjustment than males did. Similar positive association was observed with being in the more deprived Townsend quintiles [Townsend 5 (most deprived) compared to Townsend 1 (least deprived): 1.57 mmol/mol (95% CI 0.89 to 2.26)], smoking [current smoker vs non-smoker; 1.09 mmol/mol (95% CI 0.56 to 1.62)], having heart failure or on prescribed anti-heart-failure medication 1.25 mmol/mol (95% CI 0.52 to 1.99) and prescribed antidepressant medication 1.16 mmol/mol (95% CI 0.60 to 1.72) or statins 0.65 mmol/mol (95% CI 0.14 to 1.15) (Table 7.5).

A negative association was observed with increasing age; -0.20 mmol/mol (95% CI -0.22 to -0.18) in the multivariable analysis. This suggested that for every 1 year unit increase in age, a 0.20 mmol/mol decrease was observed in the final recorded HbA1c, after adjusting for other significant variables. A similar negative association was also observed with those having a history of having excessive alcohol intake -1.53 mmol/mol (95% CI -2.13 to -0.94), liver disease-1.43 mmol/mol (95% CI -2.52 to -0.34), being prescribed diuretics -1.28 mmol/mol (95% CI -1.80 to -0.76) and prescribed either oral or intravenous steroids: -1.31 mmol/mol (95% CI -2.25 to -0.36).

Table 7.5 Linear Regression using final recorded HbA1c (earliest HbA1c recording 9-18 months after index date) as the outcome

	Unadjusted (95% CI)	**Adjusted for baseline HbA1c (95% CI)**	**Adjusted for Sex, Age, Baseline HbA1c** (95% CI)**	**Fully Adjusted Multivariable¥ (95% CI)**
Baseline HbA1c (mmol/mol)	0.30 (0.29 to 0.31)	NA	NA	0.28 (0.27 to 0.29)
Baseline weight (kg)	0.06 (0.05 to 0.08)	0.05 (0.04 to 0.06)	**0.03 (0.02 to 0.04)**	0.02 (0.01 to 0.03)
Age at index date (years)	-0.29 (-0.31 to -0.28)	-0.22 (-0.24 to -0.20)	NA	-0.20 (-0.22 to -0.18)
F2FC*	0.08 (0.04 to 0.12)	0.11 (0.07 to 0.15)	**0.12 (0.08 to 0.16)**	0.08 (0.04 to 0.12)
Year Entry				
2007	Ref	Ref	Ref	Ref
2008	-0.47 (-1.36 to 0.42)	-0.33 (-1.18 to 0.51)	**-0.31 (-1.14 to 0.52)**	-0.49 (-1.33 to 0.36)
2009	-0.56 (-1.41 to 0.29)	0.06 (-0.75 to 0.87)	**0.20 (-0.60 to 0.99)**	0.22 (-0.59 to 1.03)
2010	-0.67 (-1.51 to 0.17)	0.05 (-0.75 to 0.84)	**0.22 (-0.56 to 1.01)**	0.23 (-0.58 to 1.03)
2011	0.78 (-0.09 to 1.64)	1.04 (0.22 to 1.86)	**1.02 (0.22 to 1.83)**	0.93 (0.10 to 1.76)
2012	1.05 (0.17 to 1.93)	0.91 (0.08 to 1.74)	**0.96 (0.14 to 1.78)**	0.83 (-0.01 to 1.67)
2013	0.80 (-0.12 to 1.71)	0.29 (-0.57 to 1.16)	**0.42 (-0.43 to 1.28)**	0.16 (-0.72 to 1.03)
2014	1.33 (-0.70 to 3.35)	0.26 (-1.66 to 2.17)	**0.45 (-1.43 to 2.34)**	0.19 (-1.75 to 2.14)
Sex				
Male	Ref	Ref	NA	Ref
Female	1.11 (0.67 to 1.54)	1.49 (1.08 to 1.90)	NA	1.62 (1.16 to 2.08)
Townsend Quintile				
1 (least deprived)	Ref	Ref	**Ref**	Ref
2	0.70 (0.04 to 1.36)	0.59 (-0.03 to 1.21)	**0.58 (-0.03 to 1.19)**	0.50 (-0.12 to 1.12)
3	1.57 (0.92 to 2.23)	1.16 (0.55 to 1.78)	**0.76 (0.15 to 1.37)**	0.49 (-0.12 to 1.11)
4	2.27 (1.61 to 2.93)	1.81 (1.18 to 2.44)	**1.17 (0.55 to 1.79)**	0.82 (0.18 to 1.45)
5 (most deprived)	3.47 (2.76 to 4.18)	2.90 (2.22 to 3.57)	**2.09 (1.42 to 2.76)**	1.57 (0.89 to 2.26)
Smoking Status				
Non	Ref	Ref	**Ref**	Ref
Ex	-1.03 (-1.53 to -0.54)	-0.86 (-1.33 to -0.40)	**0.15 (-0.32 to 0.62)**	0.10 (-0.39 to 0.58)
Current	2.58 (2.04 to 3.12)	1.54 (1.03 to 2.05)	**1.32 (0.81 to 1.83)**	1.09 (0.56 to 1.62)
CKD Stage				
(CrCl>60 ml/min)	Ref	Ref	Ref	
(CrCl 30-59 ml/min)	-3.38 (-3.95 to -2.80)	-2.40 (-2.95 to -1.85)	-0.06 (-0.64 to 0.52)	
(CrCl<30 ml/min)	-5.29 (-9.91 to -0.68)	-2.82 (-7.17 to 1.53)	1.79 (-2.52 to 6.10)	
Metformin Dose at Baseline				
<1500mg	Ref	Ref	**Ref**	Ref
≥1500mg	0.11 (-0.39 to 0.61)	1.05 (0.57 to 1.52)	**0.81 (0.34 to 1.28)**	0.83 (0.34 to 1.31)
Binary Comorbidity Indicator Variables				
Excessive alcohol intake	-1.41 (-2.02 to -0.80)	-1.51 (-2.08 to -0.93)	**-1.35 (-1.93 to -0.78)**	-1.53 (-2.13 to -0.94)
History of Hypoglycaemia	2.42 (0.06 to 4.78)	2.21 (-0.01 to 4.42)	**2.10 (-0.07 to 4.28)**	2.00 (-0.18 to 4.19)
Neuropathy	-0.64 (-1.73 to 0.45)	0.31 (-0.72 to 1.35)	**1.21 (0.19 to 2.23)**	0.97 (-0.08 to 2.02)
Retinopathy	-1.08 (-1.69 to -0.46)	-0.18 (-0.75 to 0.40)	0.25 (-0.31 to 0.82)	
Cardiovascular disease	-2.08 (-2.55 to -1.61)	-1.23 (-1.68 to -0.79)	**0.50 (0.04 to 0.95)**	
Heart failure	-1.21 (-1.87 to -0.54)	-0.95 (-1.59 to -0.32)	**0.90 (0.26 to 1.54)**	1.25 (0.52 to 1.99)
Anaemias	0.38 (-0.38 to 1.13)	1.07 (0.35 to 1.78)	**0.84 (0.13 to 1.55)**	0.74 (0.00 to 1.48)
Dementia	-1.42 (-4.18 to 1.34)	-2.16 (-4.81 to 0.49)	1.15 (-1.48 to 3.77)	
Liver disease	-0.31 (-1.45 to 0.84)	-0.66 (-1.74 to 0.41)	**-1.11 (-2.17 to -0.05)**	-1.43 (-2.52 to -0.34)
Arrythmias	-1.54 (-2.34 to -0.73)	-1.00 (-1.77 to	**1.14 (0.37 to 1.91)**	

	Unadjusted (95% CI)	Adjusted for baseline HbA1c (95% CI)	Adjusted for Sex, Age, Baseline HbA1c** (95% CI)	Fully Adjusted Multivariable¥ (95% CI)
		-0.24)		
Cancer	-1.83 (-2.44 to -1.22)	-1.05 (-1.63 to -0.47)	0.21 (-0.37 to 0.79)	
Hypothyroidism	0.27 (-0.49 to 1.04)	0.36 (-0.36 to 1.09)	0.45 (-0.27 to 1.18)	
Hyperthyroid	0.09 (-1.72 to 1.89)	0.08 (-1.64 to 1.79)	0.13 (-1.56 to 1.82)	
Pancreatitis	3.47 (1.65 to 5.29)	1.71 (-0.03 to 3.45)	**1.86 (0.16 to 3.57)**	
Binary Treatment Indicator Variables				
Anti-hypertensive	-2.95 (-3.41 to -2.49)	-1.53 (-1.97 to -1.09)	-0.11 (-0.55 to 0.34)	
Antiplatelets	-2.02 (-2.45 to -1.58)	-0.89 (-1.31 to -0.48)	**0.36 (-0.06 to 0.78)**	
Anticoagulants	-0.86 (-1.88 to 0.17)	-0.64 (-1.61 to 0.33)	**1.48 (0.52 to 2.45)**	
Anti-arrythmic	-2.14 (-4.73 to 0.46)	-1.00 (-3.47 to 1.47)	0.50 (-1.94 to 2.93)	
Diuretics	-2.55 (-3.02 to -2.07)	-1.87 (-2.32 to -1.42)	**-0.68 (-1.14 to -0.22)**	-1.28 (-1.80 to -0.76)
Statins	-1.59 (-2.10 to -1.08)	0.11 (-0.38 to 0.60)	**0.90 (0.41 to 1.38)**	0.65 (0.14 to 1.15)
Other lipid lowering drugs	-0.55 (-1.49 to 0.40)	0.2 (-0.70 to 1.10)	0.31 (-0.57 to 1.19)	
Antidepressants	2.67 (2.11 to 3.22)	2.29 (1.77 to 2.82)	**1.63 (1.1 to 2.15)**	1.16 (0.60 to 1.72)
Antipsychotics	2.26 (0.76 to 3.76)	0.77 (-0.66 to 2.21)	-0.40 (-1.81 to 1.02)	
Antiobesity	2.79 (1.06 to 4.52)	3.43 (1.79 to 5.08)	1.20 (-0.43 to 2.82)	
Steroids (oral/intravenous)	-1.37 (-2.32 to -0.41)	-1.73 (-2.65 to -0.81)	**-0.88 (-1.79 to 0.03)**	-1.31 (-2.25 to -0.36)
Thyroxine	0.24 (-0.53 to 1.01)	0.38 (-0.35 to 1.11)	0.52 (-0.22 to 1.25)	
Anti-thyroid drugs	2.95 (-2.91 to 8.81)	4.18 (-1.48 to 9.84)	3.83 (-1.74 to 9.39)	
Anxiolytics	0.60 (-0.35 to 1.56)	0.33 (-0.58 to 1.24)	0.16 (-0.74 to 1.06)	

*Mean Face to Face Consultation Frequency per year
**All variables in bold in the fourth column are those significant at p<0.1 level
¥Mutually adjusted for baseline HbA1c, age, year entry, F2FC, sex, Townsend quintile, smoking status, history of excessive alcohol intake, heart failure, pancreatitis, and having a prescription within 3 months prior to the index date for diuretics and antidepressant medication. All variables mutually adjusted for here are significant at the p<0.1 level after multivariable adjustment
Year entry=Year of initiation of add-on treatment, CKD=Chronic Kidney Disease, CrCL=Creatinine Clearance, Excessive alcohol intake=History of alcohol intake exceeding 35 units for male or 28 units for females.

7.4.3.2 Change in weight from baseline

The results of the regression analyses with the final weight being used as the outcome are shown in Table 7.6 below. The final weight used was the earliest recorded weight for each individual between 9-18 months after the index date. In total, 19,239 individuals [3,315 (76.1%) of all individuals prescribed sitagliptin and 15,924 (75.1%) of all prescribed sulphonylureas] had a baseline weight and final weight value recorded.

After adjusting for other covariates in the multivariable analysis, a positive association was found to exist with baseline weight: 0.97 kg (95% CI 0.96 to 0.97). This indicated that for every 1 kilogram unit increase in baseline weight, a 0.97 kilogram increase was observed in the final recorded weight, after adjusting for other significant variables. A positive association was also observed

between final weight and baseline HbA1c: 0.05 kg (95% CI 0.04 to 0.05) as shown in bold in Table 7.6

Conversely, a negative association was observed with final recorded weight and being female compared to male: -1.46 kg (95% CI -1.62 to -1.29). This indicated that being female compared to male led to a decrease of 1.46 kilograms in the final recorded weight, after adjusting for other variables. Similar negative association was observed with having a history of Chronic Kidney Disease (CKD) with Creatinine Clearance estimated between 30-59 ml/min compared to having no history of CKD: -0.36 kg (95% CI -0.59 to -0.14), having a history of heart failure -0.39 kg (95% CI -0.66 to -0.12), prescribed anticoagulants -0.76 kg (95% CI-1.16 to -0.36), or on prescribed anti-psychotics -0.68 kg (95% CI -1.22 to -0.14) or prescribed oral or intravenous steroids at baseline -0.42 kg (95% CI -0.78 to -0.06).

Table 7.6 Linear Regression using final recorded weight (earliest weight recording 9-18 months after index date) as the outcome

	Unadjusted (95% CI)	**Adjusted for baseline weight (95% CI)**	**Adjusted for Sex, Age, Baseline weight** (95% CI)**	**Fully Adjusted Multivariate¥ (95% CI)**
Baseline weight (Kg)	0.98 (0.98 to 0.99)	NA	NA	0.97 (0.96 to 0.97)
Baseline HbA1c (mmol/mol)	0.12 (0.10 to 0.13)	0.05 (0.04 to 0.05)	**0.04 (0.04 to 0.05)**	0.05 (0.04 to 0.05)
Age at index date (years)	-0.57 (-0.59 to -0.54)	-0.04 (-0.05 to -0.03)	NA	-0.02 (-0.03 to -0.02)
F2FC*	0.00 (-0.06 to 0.06)	-0.05 (-0.07 to -0.04)	**-0.03 (-0.05 to -0.01)**	-0.02 (-0.03 to 0.00)
Year Entry				
2007	Ref	Ref	Ref	Ref
2008	1.48 (0.27 to 2.70)	-0.07 (-0.39 to 0.25)	**-0.05 (-0.37 to 0.27)**	-0.06 (-0.38 to 0.25)
2009	1.79 (0.63 to 2.96)	-0.19 (-0.50 to 0.12)	**-0.16 (-0.47 to 0.15)**	-0.07 (-0.38 to 0.23)
2010	1.21 (0.05 to 2.36)	-0.76 (-1.07 to -0.45)	**-0.72 (-1.03 to -0.42)**	-0.62 (-0.92 to -0.32)
2011	0.81 (-0.38 to 1.99)	-0.99 (-1.31 to -0.68)	**-0.99 (-1.31 to -0.68)**	-0.96 (-1.27 to -0.65)
2012	1.54 (0.33 to 2.76)	-1.25 (-1.57 to -0.92)	**-1.26 (-1.58 to -0.94)**	-1.37 (-1.69 to -1.05)
2013	1.09 (-0.19 to 2.37)	-0.94 (-1.28 to -0.60)	**-0.91 (-1.25 to -0.57)**	-0.99 (-1.32 to -0.66)
2014	2.23 (-0.75 to 5.21)	-0.92 (-1.72 to -0.13)	**-0.93 (-1.72 to -0.15)**	-1.14 (-1.91 to -0.36)
Sex				
Male	Ref	Ref	NA	Ref
Female	-12.19 (-12.76 to -11.62)	-1.58 (-1.74 to -1.41)	NA	-1.46 (-1.62 to -1.29)
Townsend Quintile				
1 (least deprived)	Ref	Ref	Ref	
2	0.57 (-0.34 to 1.48)	0.04 (-0.21 to 0.28)	0.11 (-0.13 to 0.35)	
3	1.52 (0.61 to 2.42)	0.02 (-0.23 to 0.26)	0.07 (-0.17 to 0.31)	
4	2.36 (1.44 to 3.28)	-0.09 (-0.34 to 0.16)	-0.05 (-0.30 to 0.19)	
5 (most deprived)	2.13 (1.14 to 3.11)	0.06 (-0.20 to 0.32)	0.06 (-0.20 to 0.33)	
Smoking Status				
Non	Ref	Ref	Ref	
Ex	3.3 (2.62 to 3.98)	-0.01 (-0.19 to 0.18)	-0.12 (-0.31 to 0.06)	
Current	2.98 (2.24 to 3.72)	0.23 (0.03 to 0.43)	-0.05 (-0.24 to 0.15)	
CKD Stage				
(CrCl>60 ml/min)	Ref	Ref	**Ref**	Ref
(CrCl 30-59 ml/min)	-10.82 (-11.60 to -10.04)	-0.92 (-1.14 to -0.70)	**-0.35 (-0.58 to -0.12)**	-0.36 (-0.59 to -0.14)

	Unadjusted (95% CI)	Adjusted for baseline weight (95% CI)	Adjusted for Sex, Age, Baseline weight** (95% CI)	Fully Adjusted Multivariate¥ (95% CI)
(CrCl<30 ml/min)	-31.73 (-38.18 to -25.28)	-0.27 (-2.00 to 1.46)	**0.74 (-0.97 to 2.46)**	0.98 (-0.72 to 2.68)
Metformin Dose at Baseline				
<1500mg	Ref	Ref	**Ref**	
≥1500mg	2.51 (1.82 to 3.20)	-0.06 (-0.24 to 0.13)	-0.14 (-0.32 to 0.05)	
Binary Comorbidity Indicator Variables				
Excessive alcohol intake	5.08 (4.25 to 5.91)	0.52 (0.29 to 0.74)	0.08 (-0.14 to 0.31)	
History of Hypoglycaemia	-2.36 (-5.60 to 0.88)	0.33 (-0.53 to 1.19)	0.37 (-0.47 to 1.22)	
Neuropathy	1.03 (-0.48 to 2.55)	-0.07 (-0.47 to 0.33)	0.17 (-0.23 to 0.57)	
Retinopathy	-1.24 (-2.08 to -0.39)	0.01 (-0.22 to 0.23)	0.05 (-0.17 to 0.27)	
Cardiovascular disease	-1.52 (-2.16 to -0.87)	-0.49 (-0.67 to -0.32)	**-0.31 (-0.48 to -0.13)**	
Heart failure	1.78 (0.85 to 2.70)	-1.05 (-1.30 to -0.80)	**-0.58 (-0.83 to -0.32)**	-0.39 (-0.66 to -0.12)
Anaemias	-5.21 (-6.25 to -4.17)	-0.56 (-0.84 to -0.28)	-0.08 (-0.36 to 0.20)	
Dementia	-9.63 (-13.73 to -5.52)	-1.41 (-2.52 to -0.29)	-0.88 (-1.99 to 0.22)	
Liver disease	1.31 (-0.27 to 2.9)	0.07 (-0.35 to 0.49)	-0.03 (-0.45 to 0.38)	
Arrythmias	-1.04 (-2.16 to 0.08)	-0.90 (-1.20 to -0.60)	**-0.61 (-0.91 to -0.31)**	
Cancer	-4.13 (-4.98 to -3.29)	-0.55 (-0.78 to -0.32)	**-0.19 (-0.42 to 0.03)**	
Hypothyroidism	-3.06 (-4.12 to -1.99)	-0.93 (-1.22 to -0.65)	**-0.28 (-0.56 to 0.01)**	
Hyperthyroid	-5.58 (-8.11 to -3.05)	-1.27 (-1.94 to -0.60)	**-0.64 (-1.30 to 0.03)**	
Pancreatitis	-6.05 (-8.63 to -3.48)	-0.15 (-0.85 to 0.54)	-0.33 (-1.02 to 0.35)	
Binary Treatment Indicator Variables				
Anti-hypertensive	2.18 (1.55 to 2.82)	-0.48 (-0.65 to -0.31)	**-0.14 (-0.32 to 0.03)**	
Antiplatelets	-1.48 (-2.08 to -0.88)	-0.01 (-0.17 to 0.15)	0.10 (-0.06 to 0.27)	
Anticoagulants	0.90 (-0.52 to 2.32)	-1.24 (-1.62 to -0.86)	**-0.93 (-1.31 to -0.55)**	-0.76 (-1.16 to -0.36)
Anti-arrythmic	2.8 (-0.82 to 6.43)	-0.88 (-1.86 to 0.09)	-0.76 (-1.72 to 0.20)	
Diuretics	0.99 (0.33 to 1.65)	-0.56 (-0.73 to -0.38)	-0.05 (-0.23 to 0.13)	
Statins	-1.18 (-1.88 to -0.48)	-0.28 (-0.47 to -0.10)	**-0.18 (-0.37 to 0.00)**	
Other lipid lowering drugs	-1.21 (-2.50 to 0.08)	-0.21 (-0.55 to 0.13)	-0.22 (-0.56 to 0.12)	
Antidepressants	2.31 (1.54 to 3.08)	-0.4 (-0.61 to -0.19)	**-0.18 (-0.39 to 0.02)**	
Antipsychotics	0.42 (-1.63 to 2.46)	-0.64 (-1.18 to -0.09)	**-0.63 (-1.16 to -0.09)**	-0.68 (-1.22 to -0.14)
Antiobesity	19.29 (16.99 to 21.58)	-0.31 (-0.93 to 0.30)	-0.09 (-0.70 to 0.51)	
Steroids (oral/intravenous)	-4.32 (-5.65 to -2.99)	-0.81 (-1.17 to -0.45)	**-0.45 (-0.81 to -0.1)**	-0.42 (-0.78 to -0.06)
Thyroxine	-2.75 (-3.83 to -1.67)	-0.92 (-1.21 to -0.63)	-0.24 (-0.53 to 0.05)	
Anti-thyroid drugs	-5.64 (-13.93 to 2.64)	0.16 (-2.02 to 2.33)	0.52 (-1.62 to 2.67)	
Anxiolytics	-0.81 (-2.14 to 0.52)	-0.31 (-0.67 to 0.05)	-0.09 (-0.44 to 0.27)	

*Mean Face to Face Consultation Frequency per year

**All variables in bold in the fourth column are those significant at p<0.1 level

¥Mutually adjusted for baseline weight, baseline HbA1c, age, year entry, F2FC, sex, CKD stage, history of heart failure and having a prescription within 3 months prior to the index date for anticoagulants, antipsychotics and oral or intravenous steroid medication. All variables mutually adjusted for here are significant at the p<0.1 level after multivariable adjustment.

Year entry=Year of initiation of add-on treatment, CKD=Chronic Kidney Disease, CrCL=Creatinine Clearance, Excessive alcohol intake=History of alcohol intake exceeding 35 units for male or 28 units for females.

7.4.3.3 Time to first recording of a HbA1c >58 mmol/mol

In total, 26,844 (4,630 prescribed sitagliptin and 22,214 prescribed sulphonylureas) were included in the cohort for this analysis. During 30 months of follow-up, 16,419 (61.2%) of the entire cohort of 26,844 individuals recorded a HbA1c > 58 mmol/mol.

After adjusting for other covariates considered, a positive statistical association was found to exist between having a recording of a HbA1c > 58 mmol/mol and being female compared to male [Hazard Ratio (HR) 1.16 95% CI 1.12 to 1.20] (Table 7.7). This indicated that female individuals had a 16% higher risk of having a HbA1c > 58 mmol/mol being recorded after the index date compared to male individuals, having adjusted for other significant covariates. A similar positive association was also observed with baseline HbA1c (HR 1.01 95% CI 1.01 to 1.02), smoking [current smoker vs non-smoker: (HR 1.09 95% CI 1.04 to 1.13)], having a history of heart failure (HR 1.14 95% CI 1.07 to 1.21), and being prescribed antidepressants (HR 1.08 95% CI 1.03 to 1.13)

Additionally, a negative association was found to exist between having a recording of a HbA1c > 58 mmol/mol and age: (HR 0.98 95% CI 0.98 to 0.99). This indicated that for every 1 year increase in age, a 2% lower risk of having a HbA1c recorded of > 58 mmol/mol was observed after adjustment. A similar negative association was observed with having a history of excessive alcohol intake (HR 0.90 95% CI 0.86 to 0.95) and prescribed diuretics (HR 0.88 95% CI 0.85 to 0.92).

Table 7.7 Cox regression using the time to first recording of a HbA1c > 58 mmol/mol as the outcome

	Unadjusted HR (95% CI)	**Adjusted for Sex, Age HR** (95% CI)**	**Fully Adjusted Multivariate¥ HR (95% CI)**
Baseline HbA1c (mmol/mol)	1.01 (1.01 to 1.01)	**1.01 (1.01 to 1.01)**	1.01 (1.01 to 1.02)
Baseline weight (kg)	1.01 (1.00 to 1.01)	**1.00 (1.00 to 1.01)**	1.00 (1.00 to 1.01)
Age at index date (years)	0.98 (0.98 to 0.98)	NA	0.98 (0.98 to 0.99)
F2FC*	1.01 (1.01 to 1.02)	**1.01 (1.01 to 1.02)**	1.01 (1.01 to 1.02)
Year Entry			
2007	Ref	**Ref**	Ref
2008	1.00 (0.94 to 1.07)	**1.00 (0.94 to 1.07)**	1.02 (0.95 to 1.09)
2009	0.95 (0.89 to 1.01)	**0.95 (0.89 to 1.01)**	1.00 (0.93 to 1.06)
2010	0.96 (0.9 to 1.02)	**0.96 (0.90 to 1.02)**	1.00 (0.94 to 1.07)
2011	1.03 (0.97 to 1.10)	**1.03 (0.97 to 1.10)**	1.05 (0.98 to 1.12)
2012	1.06 (0.99 to 1.13)	**1.06 (0.99 to 1.13)**	1.05 (0.98 to 1.12)
2013	0.97 (0.91 to 1.04)	**0.97 (0.91 to 1.04)**	0.94 (0.87 to 1.01)

	Unadjusted HR (95% CI)	Adjusted for Sex, Age HR** (95% CI)	Fully Adjusted Multivariate¥ HR (95% CI)
2014	0.99 (0.89 to 1.09)	**0.99 (0.89 to 1.09)**	0.94 (0.85 to 1.04)
Sex			
Male	Ref	NA	Ref
Female	1.11 (1.07 to 1.14)	NA	1.16 (1.12 to 1.20)
Townsend Quintile			
1 (least deprived)	Ref	**Ref**	Ref
2	1.02 (0.98 to 1.08)	**1.02 (0.97 to 1.07)**	1.02 (0.97 to 1.07)
3	1.05 (1.00 to 1.10)	**1.01 (0.96 to 1.06)**	1.01 (0.96 to 1.06)
4	1.10 (1.05 to 1.15)	**1.04 (0.99 to 1.09)**	1.04 (0.99 to 1.09)
5 (most deprived)	1.19 (1.13 to 1.25)	**1.11 (1.05 to 1.17)**	1.11 (1.05 to 1.17)
Smoking Status			
Non	Ref	**Ref**	Ref
Ex	0.96 (0.93 to 1.00)	**1.05 (1.01 to 1.09)**	1.04 (1.00 to 1.08)
Current	1.16 (1.12 to 1.21)	**1.13 (1.09 to 1.18)**	1.09 (1.04 to 1.13)
CKD Stage			
(CrCl>60 ml/min)	Ref	**Ref**	
(CrCl 30-59 ml/min)	0.77 (0.74 to 0.81)	**0.94 (0.90 to 0.99)**	
(CrCl<30 ml/min)	0.72 (0.50 to 1.03)	**1.06 (0.74 to 1.53)**	
Metformin Dose at Baseline			
<1500mg	Ref	Ref	
≥1500mg	0.99 (0.95 to 1.03)	0.98 (0.94 to 1.02)	
Binary Comorbidity Indicator Variables			
Excessive alcohol intake	0.89 (0.86 to 0.94)	**0.9 (0.86 to 0.95)**	0.90 (0.86 to 0.95)
History of Hypoglycaemia	1.17 (0.99 to 1.38)	**1.18 (1.00 to 1.40)**	1.18 (1.04 to 1.34)
Neuropathy	0.94 (0.86 to 1.01)	1.02 (0.94 to 1.11)	
Retinopathy	0.96 (0.92 to 1.00)	1.00 (0.96 to 1.05)	
Cardiovascular disease	0.9 (0.87 to 0.93)	**1.05 (1.01 to 1.09)**	
Heart failure	0.96 (0.91 to 1.01)	**1.13 (1.08 to 1.19)**	1.14 (1.07 to 1.21)
Anaemias	1.03 (0.98 to 1.09)	1.03 (0.98 to 1.09)	
Dementia	0.87 (0.71 to 1.06)	1.16 (0.95 to 1.42)	
Liver disease	1.05 (0.97 to 1.14)	1.02 (0.94 to 1.11)	
Arrythmias	0.94 (0.89 to 1.00)	**1.13 (1.07 to 1.21)**	
Cancer	0.89 (0.85 to 0.93)	1.00 (0.95 to 1.05)	
Hypothyroidism	1.01 (0.96 to 1.07)	**1.03 (0.97 to 1.09)**	
Hyperthyroid	1.04 (0.91 to 1.18)	1.05 (0.91 to 1.19)	
Pancreatitis	1.17 (1.03 to 1.32)	**1.18 (1.04 to 1.34)**	
Binary Treatment Indicator Variables			
Anti-hypertensive	0.85 (0.82 to 0.88)	**0.97 (0.94 to 1.00)**	
Antiplatelets	0.88 (0.85 to 0.91)	0.99 (0.96 to 1.02)	
Anticoagulants	0.98 (0.91 to 1.06)	**1.18 (1.09 to 1.28)**	
Anti-arrythmic	0.85 (0.7 to 1.04)	0.97 (0.79 to 1.18)	
Diuretics	0.84 (0.81 to 0.87)	**0.94 (0.91 to 0.97)**	0.88 (0.85 to 0.92)
Statins	0.95 (0.91 to 0.98)	1.03 (0.99 to 1.07)	
Other lipid lowering drugs	1.02 (0.96 to 1.09)	1.04 (0.97 to 1.11)	
Antidepressants	1.2 (1.16 to 1.25)	**1.15 (1.1 to 1.19)**	1.08 (1.03 to 1.13)
Antipsychotics	1.12 (1.01 to 1.24)	1.02 (0.92 to 1.14)	
Antiobesity	1.16 (1.03 to 1.31)	0.97 (0.86 to 1.09)	
Steroids (oral/intravenous)	0.97 (0.91 to 1.04)	1.04 (0.97 to 1.12)	
Thyroxine	1.01 (0.95 to 1.07)	1.03 (0.97 to 1.09)	
Anti-thyroid drugs	1.03 (0.66 to 1.61)	1.02 (0.65 to 1.60)	
Anxiolytics	1.02 (0.95 to 1.09)	1.01 (0.95 to 1.08)	

*Mean Face to Face Consultation Frequency per year
**All variables in bold in the third column are those significant at p<0.1 level
¥Mutually adjusted for baseline HbA1c, age, year entry, F2FC, sex, Townsend Quintile, smoking status, history of excessive alcohol intake, heart failure, pancreatitis, and having a prescription within 3 months prior to the index date for diuretics and antidepressant medication. All variables mutually adjusted for are significant at the p<0.1 level after multivariable adjustment.
HR=Hazard Ratio, Year entry=Year of initiation of add-on treatment, CKD=Chronic Kidney Disease, CrCL=Creatinine Clearance, Excessive alcohol intake=History of alcohol intake exceeding 35 units for male or 28 units for females.

7.4.3.4 Time to first recording of an anti-diabetic treatment regimen change

In total, 26,844 (4,630 prescribed sitagliptin and 22,214 prescribed sulphonylureas) were included in the cohort for this analysis. During 30 months of follow-up, 7,597 (28.3%) of the entire cohort of 26,844 individuals recorded an anti-diabetic treatment regimen change.

After adjusting for other covariates considered, a positive association was found to exist between having a recording of a treatment regimen change and being female compared to male [Hazard Ratio (HR) 1.28 95% CI 1.21 to 1.34] (Table 7.8). This indicated that female individuals had a 28% higher risk of having a treatment regimen change after the index date compared to male individuals, having adjusted for other covariates. A similar positive association was also observed with baseline HbA1c (HR 1.01 95% CI 1.01 to 1.02), smoking [current smoker vs non-smoker: (HR 1.11 95% CI 1.05 to 1.18)], having a history of heart failure (HR 1.17 95% CI 1.06 to 1.28) and being prescribed other lipid lowering drugs (HR 1.13 95% CI 1.02 to 1.26), antidepressants (HR 1.15 95% CI 1.08 to 1.22) and anti-obesity medication (HR 1.26 95% CI 1.08 to 1.47).

Additionally, a negative association was found to exist between having a recording of a treatment change and age: (HR 0.98 95% CI 0.97 to 0.98). This indicated that for every 1 year increase in age, a 2% lower risk of having a recording of a treatment change was observed after adjustment. A similar negative association was observed with having a history of being prescribed diuretics (HR 0.92 95% CI 0.87 to 0.99).

Table 7.8 Cox Regression using time to first recording of an anti-diabetic treatment regimen change as the outcome

	Unadjusted HR (95% CI)	**Adjusted for Sex, Age HR** (95% CI)**	**Fully Adjusted Multivariable HR¥ (95% CI)**
Baseline HbA1c (mmol/mol)	1.01 (1.01 to 1.02)	**1.01 (1.01 to 1.01)**	1.01 (1.01 to 1.02)
Baseline weight (kg)	1.01 (1.01 to 1.01)	**1.01 (1.00 to 1.01)**	1.00 (1.00 to 1.01)
Age at index date (years)	0.97 (0.97 to 0.97)	NA	0.98 (0.97 to 0.98)
F2FC*	1.03 (1.02 to 1.03)	**1.03 (1.02 to 1.03)**	1.02 (1.02 to 1.03)
Year Entry			
2007	Ref	**Ref**	Ref
2008	1.11 (1.00 to 1.22)	**1.11 (1.00 to 1.22)**	1.09 (0.99 to 1.21)

	Unadjusted HR (95% CI)	Adjusted for Sex, Age HR** (95% CI)	Fully Adjusted Multivariable HR¥ (95% CI)
2009	1.20 (1.09 to 1.31)	**1.20 (1.09 to 1.31)**	1.26 (1.14 to 1.38)
2010	1.16 (1.06 to 1.27)	**1.16 (1.06 to 1.27)**	1.24 (1.12 to 1.36)
2011	1.16 (1.05 to 1.27)	**1.16 (1.05 to 1.27)**	1.16 (1.05 to 1.28)
2012	1.15 (1.05 to 1.27)	**1.15 (1.05 to 1.27)**	1.14 (1.03 to 1.26)
2013	1.14 (1.03 to 1.27)	**1.14 (1.03 to 1.27)**	1.12 (1.00 to 1.25)
2014	1.24 (1.06 to 1.45)	**1.24 (1.06 to 1.45)**	1.20 (1.02 to 1.42)
Sex			
Male	Ref	NA	Ref
Female	1.19 (1.13 to 1.24)	NA	1.28 (1.21 to 1.34)
Townsend Quintile			
1 (least deprived)	Ref	Ref	
2	1.05 (0.97 to 1.12)	1.04 (0.97 to 1.12)	
3	1.12 (1.04 to 1.2)	1.06 (0.98 to 1.13)	
4	1.13 (1.05 to 1.21)	1.03 (0.95 to 1.10)	
5 (most deprived)	1.19 (1.1 to 1.29)	1.06 (0.98 to 1.14)	
Smoking Status			
Non	Ref	**Ref**	Ref
Ex	0.98 (0.93 to 1.04)	**1.14 (1.07 to 1.20)**	1.08 (1.02 to 1.15)
Current	1.25 (1.18 to 1.32)	**1.20 (1.14 to 1.27)**	1.11 (1.05 to 1.18)
CKD Stage			
(CrCl>60 ml/min)	Ref	Ref	
(CrCl 30-59 ml/min)	0.70 (0.65 to 0.75)	0.96 (0.89 to 1.03)	
(CrCl<30 ml/min)	0.64 (0.36 to 1.13)	1.21 (0.68 to 2.13)	
Metformin Dose at Baseline			
<1500mg	Ref	Ref	
≥1500mg	1.00 (0.94 to 1.05)	0.98 (0.93 to 1.03)	
Binary Comorbidity Indicator Variables			
Excessive alcohol intake	0.92 (0.86 to 0.99)	0.95 (0.89 to 1.02)	
History of Hypoglycaemia	1.09 (0.86 to 1.40)	1.10 (0.86 to 1.41)	
Neuropathy	0.97 (0.86 to 1.09)	**1.11 (0.98 to 1.25)**	
Retinopathy	0.92 (0.86 to 0.98)	0.99 (0.92 to 1.06)	
Cardiovascular disease	0.89 (0.84 to 0.93)	**1.14 (1.08 to 1.20)**	
Heart failure	1.00 (0.93 to 1.07)	**1.31 (1.22 to 1.41)**	1.17 (1.06 to 1.28)
Anaemias	1.00 (0.92 to 1.09)	0.98 (0.90 to 1.06)	
Dementia	0.67 (0.48 to 0.94)	1.06 (0.75 to 1.50)	
Liver disease	1.14 (1.01 to 1.28)	1.09 (0.97 to 1.22)	
Arrythmias	0.90 (0.82 to 0.98)	**1.22 (1.11 to 1.34)**	
Cancer	0.86 (0.81 to 0.93)	1.03 (0.96 to 1.11)	
Hypothyroidism	1.08 (0.99 to 1.17)	**1.10 (1.01 to 1.19)**	
Hyperthyroid	1.09 (0.90 to 1.32)	1.10 (0.91 to 1.33)	
Pancreatitis	1.34 (1.12 to 1.59)	**1.36 (1.14 to 1.62)**	1.17 (0.97 to 1.41)
Binary Treatment Indicator Variables			
Anti-hypertensive	0.79 (0.76 to 0.83)	0.97 (0.92 to 1.02)	
Antiplatelets	0.84 (0.80 to 0.88)	1.02 (0.97 to 1.07)	
Anticoagulants	1.03 (0.92 to 1.15)	**1.40 (1.25 to 1.57)**	1.12 (0.99 to 1.27)
Anti-arrythmic	1.11 (0.85 to 1.45)	**1.36 (1.04 to 1.78)**	
Diuretics	0.87 (0.82 to 0.91)	**1.04 (0.98 to 1.10)**	0.93 (0.87 to 0.99)
Statins	0.87 (0.82 to 0.91)	0.99 (0.94 to 1.04)	
Other lipid lowering drugs	1.07 (0.97 to 1.18)	**1.11 (1.00 to 1.22)**	1.13 (1.02 to 1.26)
Antidepressants	1.37 (1.3 to 1.45)	**1.27 (1.20 to 1.34)**	1.15 (1.08 to 1.22)
Antipsychotics	1.25 (1.09 to 1.45)	1.08 (0.93 to 1.25)	

	Unadjusted HR (95% CI)	Adjusted for Sex, Age HR** (95% CI)	Fully Adjusted Multivariable HR¥ (95% CI)
Antiobesity	1.75 (1.51 to 2.02)	**1.32 (1.14 to 1.54)**	1.26 (1.08 to 1.47)
Steroids (oral/intravenous)	0.98 (0.88 to 1.08)	**1.10 (0.99 to 1.22)**	
Thyroxine	1.07 (0.99 to 1.16)	**1.10 (1.01 to 1.20)**	
Anti-thyroid drugs	0.88 (0.44 to 1.76)	0.88 (0.44 to 1.75)	
Anxiolytics	1.14 (1.04 to 1.25)	**1.14 (1.03 to 1.25)**	

*Mean Face to Face Consultation Frequency per year
**all variables in bold in the third column are those significant at p<0.1 level
¥Mutually adjusted for baseline HbA1c, age, year entry, F2FC, sex, Townsend Quintile, smoking status, history of excessive alcohol intake, heart failure, pancreatitis, and having a prescription within 3 months prior to the index date for diuretics and antidepressant medication. All variables mutually adjusted for here are significant at the p<0.1 level after multivariable adjustment.
HR=Hazard Ratio, Year entry=Year of initiation of add-on treatment, CKD=Chronic Kidney Disease, CrCL=Creatinine Clearance, Excessive alcohol intake=History of alcohol intake exceeding 35 units for male or 28 units for females.

7.5 Discussion

7.5.1 Summary of main findings

In this study, I found that 4,080 (88.1%) individuals initiated on sitagliptin and 20,103 (90.5%) initiated on sulphonylureas as add-on to metformin were followed up for at least 12 months. I also found that 3,613 (82.9%) on sitagliptin and 17,742 (83.7%) prescribed sulphonylureas had a final HbA1c recorded between 9 and 18 months while 3,315 (76.1%) and 15,924 (75.1%) had a final weight recorded within that time interval respectively. Equally, the vast number of recordings for a HbA1c > 58 mmol/mol [16,419 (88.9%) out of a total of 18,477], and a treatment regimen change [7,597 (72.6%) out of a total of 10,467] were within 30 months (2.5 years) of the index date.

The regression analyses revealed several associations to exist between demographic and clinical covariates and each of the four respective outcomes. These are discussed in further detail below.

7.5.2 Comparison with existing literature

7.5.2.1 HbA1c

NICE recommends HbA1c is measured at a frequency of 3–6-monthly intervals until the HbA1c is stable after commencement of a new therapy and at 6-monthly intervals once the HbA1c level is within target and stable.[22] Thus, if guidelines were strictly adhered to in clinical practice, I would expect to find a HbA1c level recorded at least every 6 months for each individual. In addition to guidance from NICE, the quality and outcomes framework introduced as part of the GP contract in 2004, financially incentivised monitoring of individuals with diabetes mellitus in general practice.[104] Since 2004, practices have been rewarded for the percentage of individuals within the practice with DM, for whom the last HbA1c was < 58 mmol/mol (7.5%), < 64 mmol/mol (8.0%) or < 75 mmol/mol (9.0%) in the preceding 15 months.[104] I found that over 80% of all individuals on

either add-on treatment at any timepoint (that had not been lost to follow-up i.e. not left their registered practice or died) had a HbA1c recorded in each 9 months interval on average, 70% in each 6 months interval (Appendix E, Supplementary Figures 7A1) while around 45% had one recorded in each 3 monthly interval. Importantly, the frequency of recording at a population level was similar across both sitagliptin and sulphonylureas cohorts for each time period. In order to maximise the use of reported HbA1c, the first HbA1c recorded between 9-18 months after the index date was used as the final HbA1c in the regression analyses.

Several covariates were found to be associated with a significant increase in the value of the final recorded HbA1c; baseline HbA1c, being a smoker, being in the most deprived Townsend quintile, having heart failure or on prescribed antidepressant medication or statins. For example, a 1 mmol/mol increase in baseline HbA1c was associated with a 0.28 mmol/mol (95% CI 0.27-0.29) increase in final HbA1c after adjusting for other significant covariates. An increase of 1.09 mmol/mol (95% CI 0.56-1.62) was also observed in the final HbA1c among those individuals recorded as being a "current smoker" at baseline compared to a "non-smoker". No study quantifying the exact increase seen among individuals who smoked and HbA1c was identified in literature for comparison. However, in a large US prospective cohort study of more than 1 million participants, Will et al found that the new incidence of diabetes mellitus increased among both men and women who smoked.[142,143] In this study, I found that those from more socially deprived areas [Townsend 5 compared to Townsend 1] had a higher final HbA1c by about 1.57 mmol/mol (95% CI 0.89-2.26). Once again, no quantitative comparison was available in the literature, however a significant relationship between social deprivation and worsening diabetes, specifically diabetes related mortality, has been described previously by Saydah et al.[113] I also found an increase of around 1.25 mmol/mol (95% CI 0.52-1.99) in HbA1c among individuals who had heart failure at time of add-on initiation. Several studies, have examined the reverse link more commonly, investigating whether higher HbA1c can increase risk of heart failure. Zhao et al conducted one such study and found a positive graded association to exist between rising HbA1c and incident heart failure.[144] A statistically significant increase of 1.16 mmol/mol (95% CI 0.60-1.72) in HbA1c was associated with individuals prescribed antidepressants at baseline. This association was in contrast to the findings from a prospective cohort study with 4,700 participants by Da Silva and colleagues in 2015 where they found that use of antidepressants was not associated with altered HbA1c or glucose metabolism.[145] They suggested that the association between antidepressant use and diabetes previously reported in other studies may not be causal

but in fact simply linked to the fact that individuals prescribed antidepressants are more likely to be screened for diabetes.[145] I also found that those that had a statin prescribed at baseline, had a higher value for their final HbA1c by 0.65 mmol/mol (95% CI 0.14-1.15). Several studies have shown that statins can increase both incidence of new onset diabetes and glycaemic levels among those already diagnosed.[146,147] The PROVE-IT TIMI 22 trial showed that statin use led to an increase in HbA1c of between 1.3 mmol/mol and 3.3 mmol among individuals without pre-existing diabetes.[146] One retrospective cohort study examined increases in HbA1c after statin initiation among those with established diabetes and found that the rise in HbA1c varied between 0 mmol/mol to 3.3 mmol/mol.[147]

I also found that several covariates were associated with a statistically significantly decrease in the value of the final recorded HbA1c; age, history of heavy drinking, liver disease and being prescribed diuretics or steroids. For example, a decrease in final HbA1c of -1.53 mmol/mol (95% CI -2.13 to -0.94) was found among those with a history of excessive alcohol intake (>35 units of alcohol for men and >28 units for female). High levels of alcohol consumption have been shown to increase insulin sensitivity to a degree and decrease HbA1c moderately while also acutely increasing the risk of hypoglycaemias.[148] A history of liver disease was also shown to be associated with a lower value of the final HbA1c by -1.43 mmol/mol (95% CI -2.52 to -0.34). Lower HbA1c has been previously reported among individuals with liver disease,[149] however little has been reported about the impact of liver disease on glycaemic control in individuals who already have diabetes mellitus.[150] I also observed a decrease in HbA1c among individuals with prescribed diuretics of -1.28 mmol/mol (95% CI -1.80 to -0.76). Most previous studies report increases in HbA1c among individuals with prescribed diuretics particularly thiazides though reported increases are only moderate. For example, Hirst et al undertook a meta-analysis where they demonstrated an increase of 0.77 mmol/l (95% CI 0.14 to 1.39) in fasting blood glucose among users of thiazides.[151] However, unlike HbA1c which reflects glucose control for 2-3 months period, fasting glucose reflects control at a singular timepoint only. Equally, steroid usage is well known to increase blood glucose levels,[152] and hence my finding that it was associated with a lower final recorded HbA1c was unusual -1.31 mmol/mol (95% CI -2.25 to - 0.36). However it is possibly explained by the fact that steroid courses are usually short term and cyclical in response to disease flare ups with their effects usually being transient and reversible.[152] This is further supported in the findings of a study led by Habib et al where they investigated HbA1c changes

among a group of individuals treated with steroid for a Chronic Obstructive Pulmonary Disease flare-up who had a history of T2DM and found no significant change.[153]

7.5.2.2 Weight

NICE guidance does not specifically recommend a frequency for monitoring weight or body mass index (BMI) and in fact suggests self-monitoring is often the best option to keep individual's motivated.[137] The quality and outcomes framework financially rewards practices for having a recorded BMI in the preceding 15 months for individuals with diabetes mellitus.[104] This is also likely to have influenced weight recording in THIN. I found that less individuals had weight recorded at both 9 monthly and 3 monthly intervals compared to HbA1c. Approximately 75% of all individuals at any timepoint (that had not been lost to follow-up i.e. not left their practice or died) on both treatments had a weight recorded in each 9 months interval on average while only 35% of the total had one recorded in each 3 month interval examined. The first weight recorded between 9-18 months after the index date was therefore used as the final weight in the regression analyses.

Only baseline weight was found to significantly increase the value of the final recorded weight, with an increase of 0.97 kg (95% CI 0.96 to 0.97) observed in the final weight for every 1kg increase in baseline weight. A positive association was also observed with every 1mmol/mol increase in HbA1c of 0.05kg in the final weight recorded. HbA1c and weight are well known to be positively correlated which is why NICE guidance supports weight reduction as an integral part of management of T2DM.[22,136]

I also found that several covariates were found to be associated with a significant decrease in the value of the final recorded weight; age, having chronic kidney disease, heart failure and being prescribed anticoagulants, antipsychotics and steroids.

This association between weight loss and both kidney disease; -0.36kg (95% CI -0.59 to -0.14) and heart failure; -0.39kg (95% CI -0.66 to -0.12) was difficult to disentangle as individuals with these comorbidities suffer with body fluid imbalances which often leads to significant fluctuations in their weight.[150,154] A recent study examining weight loss in obese individuals with heart failure actually demonstrated an association with greater mortality among those who underwent ≥5% weight loss, highlighting the complexity of this population group.[155] I also found that being prescribed antipsychotics at baseline was associated with a weight reduction of around -0.68kg (95% CI -1.22 to -0.14). This finding was unusual as a recent meta-analysis concluded that nearly all anti-psychotics are associated with weight gain.[156,157] However, there is some evidence that

weight gain with antipsychotics may in fact level off over time following initiation.[156] Weight loss was also associated with usage of corticosteroids: -0.42 kg (95% CI -0.78 to -0.06). This weight change was not highly significant and trials have shown that short oral and intravenous steroid courses do not substantially affect weight.[158] No literature could be retrieved detailing the unusual association of weight loss with prescribing of anticoagulants: -0.76 (95% CI -1.16 to -0.36). This may be a chance finding for the cohort of sitagliptin and sulphonylureas users being examined in this study.

7.5.2.3 First recording of a HbA1c > 58 mmol/mol

Guidance from NICE states that recording of a HbA1c > 58 mmol/mol is indicative of poor glycaemic control.[22] I have shown that the recording frequency of HbA1c was similar across individuals prescribed sitagliptin and sulphonylureas over time. This was important as otherwise when I undertake a cohort study comparing these two add-on therapies for time to recording of first HbA1c > 58 mmol/mol in Chapter 10, there would be a risk of recording bias. I also found that the majority of individuals had their recording of HbA1c > 58 mmol/mol within 30 months (2.5 years) of treatment initiation, hence I have focused on this period for the regression analyses.

Several covariates were found to be positively associated with having a recording of a HbA1c > 58 mmol/mol: baseline HbA1c, being female, being a smoker, having heart failure or on prescribed antidepressant medication. Female individuals had a 16% higher risk (HR 1.16, 95% CI 1.12 to 1.20) of having a HbA1c > 58 mmol/mol being recorded after the index date compared to male individuals. No study was retrieved in the literature which examined the effect of gender on achieving HbA1c targets. Studies have evaluated the impact of gender on adherence to medication with T2DM reporting no major impact.[159] However, in most cases these findings may be confounded by several other factors such as socioeconomic status, for example, and hence are difficult to disentangle. The finding that higher baseline HbA1c, having heart failure (HR 1.14, 95% CI 1.07 to 1.21) and being prescribed antidepressant medication (HR 1.08, 95% CI 1.03 to 1.13) led to a higher likelihood of recording a HbA1c > 58 mmol/mol was logical, as these covariates were all also positively associated with having a higher final HbA1c value as detailed earlier.

A few covariates were also found to be negatively associated with having a recording of a HbA1c > 58 mmol/mol: age (HR 0.98, 95% CI 0.98-0.99), history of excessive alcohol intake (HR 0.90, 95% CI 0.86 to 0.95) and being prescribed diuretics (HR 0.88, 95% CI 0.85 to 0.92). I have already

described why these covariates may be linked to a reduction in recording of a HbA1c > 58 mmol/mol in the section on change in HbA1c from baseline earlier in this discussion.

7.5.2.4 First recording of an anti-diabetic treatment regimen change

NICE guidance recommends treatment change when the HbA1c exceeds 58 mmol/mol.[22] However, despite this guidance, clinical inertia in individuals with T2DM is a well-established problem with individuals remaining in suboptimal glycaemic control for long periods before treatment is actually changed. The fact that I detected 16,419 individuals with a HbA1c >58 mmol/mol recorded over 30 months (2.5 years) of follow-up however, only 7,597 with a recorded treatment regimen change provides evidence already to support this inertia.

Several covariates were found to be positively associated with having a recording of a treatment regimen change. One of the strongest predictors of treatment regimen change involved being female (HR 1.28, 1.21 to 1.34), with females having a 28% higher likelihood of change. Other predictors of treatment regimen change included higher baseline HbA1c (HR 1.01, 95% CI 1.01 to 1.02), being a smoker (HR 1.11, 95% CI 1.05 to 1.18), having a history of heart failure (HR 1.17, 95% CI 1.06 to 1.28) and being prescribed other lipid lowering drugs (HR 1.13, 95% CI 1.02 to 1.26), antidepressants (HR 1.15, 95% CI 1.08 to 1.22) and anti-obesity medication (HR 1.26, 95% CI 1.08 to 1.47).

One study undertaken using data from a United States Claims database by Lin and colleagues, also examined predictors of anti-diabetic treatment change in individuals with T2DM in general, focusing on intensification only (not on switching).[160] They also found a higher rate of intensification among those with higher HbA1c as expected. They found that those with a baseline HbA1c ≥ 75 mmol/mol had an almost 4 fold higher odds for intensification, (Odds Ratio (OR) 3.8 (95% CI 3.7 to 4.0) compared to those with a HbA1c between 53-64 mmol/mol at baseline.[160] They also found higher rates of treatment intensification among those with a history of mental illness (OR 1.2, 95% CI 1.1 to 1.2), broadly similar to my finding of a 15% higher risk of treatment change for those on anti-depressants (HR 1.15, 95% CI 1.08 to 1.22).[160] They found no major effect of gender on intensification, while other significant covariates identified in my study were not explored by Lin and colleagues.[160]

Several negative predictors for recording a treatment regimen change were also identified in my study including; age (HR 0.98, 0.97 to 0.98) and being prescribed diuretics (HR 0.93, 95% CI 0.87 to 0.99). The study undertaken by Lin and colleagues, also found a lower likelihood of intensification among older individuals with T2DM for intensification.[160] In those aged ≥ 75 years

the odds ratio for intensification was 0.6 (95% CI 0.6 to 0.7) compared to those aged 18-39 years.[160] However, they found that those prescribed diuretics had a higher probability for intensification [Odds Ratio 1.05 (95% CI 1.00 to 1.11)] which was in contrast to the findings in my study.[160] This may be due to the fact they included all individuals regardless of what anti-diabetic they were on at baseline (including those prescribed more than 3 different anti-diabetics), while I restricted my cohort to only those prescribed sitagliptin or sulphonylureas as add-on to metformin. Lin and colleagues also found treatment intensification to be higher among those who had point of service insurance and a recent endocrinologist visit, however these factors were not examined in my study and are more applicable to a US healthcare system.[160]

Another factor which might lead to a treatment regimen change is individual non-adherence to medication.[161] Therefore, one might expect that factors identified in the literature which increase non-adherence to anti-diabetics may include some of the predictors of treatment regimen change I identified as well. García-Pérez and colleagues identified polytherapy and psychological factors as two major causes for non-adherence in their narrative review of barriers to adherence in T2DM. Polytherapy leading to treatment regimen change is broadly evident in my study as well given prescribing of anti-depressants, lipid-lowering treatments and anti-obesity medication all increased likelihood of treatment change.[161]

7.6 Context of this chapter in overall work

In this chapter, I have demonstrated that recordings of HbA1c and weight over time are similar in frequency across the sitagliptin and sulphonylurea cohorts. I have also shown that by using a 9-18 month window after the index date to obtain the value for final HbA1c and weight, I will obtain a recorded final value for approximately 80% of the individuals for HbA1c and approximately 75% for weight. I have also shown that the vast majority of individuals have their first recording of an undesirable HbA1c > 58 mmol/mol and anti-diabetic treatment regimen change within 30 months (2.5 years) of initiation of add-on treatment with sitagliptin or sulphonylureas.

I have also identified and described several covariates that are strongly linked to each of the four outcomes. These covariates have already been demonstrated to be associated with the exposure in Chapter 6. Those covariates associated with both exposure and outcome will be included as confounders in the cohort studies in Chapters 9 and 10. In the next chapter, I will discuss some alternate approaches to identifying and handling confounders in observational studies using causal diagrams and propensity scores.

Chapter 8 Alternative approaches to handling the challenge of confounding in observational studies

8.1 Chapter Overview

In the previous two chapters I outlined covariates associated with the exposure (Chapter 6) and subsequently, the outcomes (Chapter 7). Covariates associated with both exposure and outcome are those which could confound the final results. Another alternative method for identifying confounders, which is driven by theoretical knowledge of factors influencing the research questions and involves use of causal diagrams will be presented in this chapter.

The most common methods of accounting for confounders once identified in observational studies is through adjustment of the individual factors using a multivariable regression analysis. In this chapter, I will describe an alternative approach to handling confounding in analysis, through use of propensity score matching methods

8.2 Background – the importance of accounting for confounding in observational studies

In clinical practice, treatment is not randomised but in fact prescribed based on the prescriber's judgment of how they perceive the treatment may influence future beneficial and adverse health outcomes.[79] For example, a prescriber may avoid prescribing sulphonylureas to improve glycaemic control if an individual has a history of hypoglycaemias as they may believe the sulphonylureas might increase their risk of hypoglycaemia further (as evidenced in literature[162]). The lack of randomisation in observational studies, means that a simple direct comparison of treated and untreated individuals for example, may lead one to erroneously conclude that treatment is harmful when in fact it may be given to those at greater risk of harm.[79] The approach to preventing such erroneous conclusions involves first carefully identifying those variables that may affect both choice of treatment and the occurrence of the outcome, otherwise known as confounding variables. Confounding variables must be carefully determined and must not be on the causal pathway between the exposure and outcome otherwise adjusting for them would actually lead to removal of the effect of the exposure itself.

In Chapter 6, I described and quantified the existence of associations between my exposure of interest (sitagliptin or sulphonylureas as add-on to metformin) and a range of measured covariates. In the subsequent Chapter 7, I described and quantified the existence of associations

between the outcomes I plan to investigate in my cohort studies and a range of measured covariates. Thus between these two chapters, I was able to identify those variables which could potentially confound my results. This method for identifying confounders is a data-driven approach and has an important place in statistical methodology as it allows one to generate the most parsimonious model for analysis and thus, the most precise final statistical estimates.[80] However, there are alternative approaches to identifying confounding in a study. One such alternative method involves a theoretical approach where the confounding variables are decided *a priori* (before undertaking the study), and justification for inclusion is often described using causal diagrams such as direct acyclic graphs (DAGs). In the first part of this chapter, I will present this alternative approach for identifying confounding using one of my proposed cohort studies as an example.

Once the confounders are identified, they must then be accounted for appropriately in analysis to ensure one gets unbiased estimates of effect. The most traditional method is by means of a regression analysis which will be my main analysis approach in the next chapter. Another increasingly used method of adjusting for confounding in observational studies involves use of propensity score matching.[163] In this chapter, I will also present the theory behind use of propensity score matching which I will undertake as a supportive analysis to my main regression analysis in Chapter 9.

8.3 Use of Direct Acyclic Graphs (DAGs) to identify confounding variables

Direct Acyclic Graphs (DAGs) represent the most common form of causal diagram used in epidemiology for depicting relationships between exposure, outcome and covariates.[164] Their use is best described by means of an example, which I illustrate below in Figure 8.1. Consider a study investigating the relationship between a new drug and the risk of lung cancer as shown in Figure 8.1. The unidirectional single headed arrows represent a direct link between a cause and effect and also the direction in which one anticipates the effect to occur e.g. “Smoking Status” and “Lung Cancer”. Using DAG terminology, “Smoking Status” here would be an ancestor or cause of effect of “Lung Cancer” and “Lung Cancer” would be an example of its descendant as it is affected by “Smoking Status”.[164,165] In such a study, “Smoking Status” may be a particularly important variable as this may affect whether the clinician decides to use the “New Drug” and also because smoking itself can increase the risk of lung cancer. “Smoking Status” is thus a confounder in the study and

unless one blocks its effect in the final analysis, the estimate for the effect of the new drug on causing lung cancer will be biased.

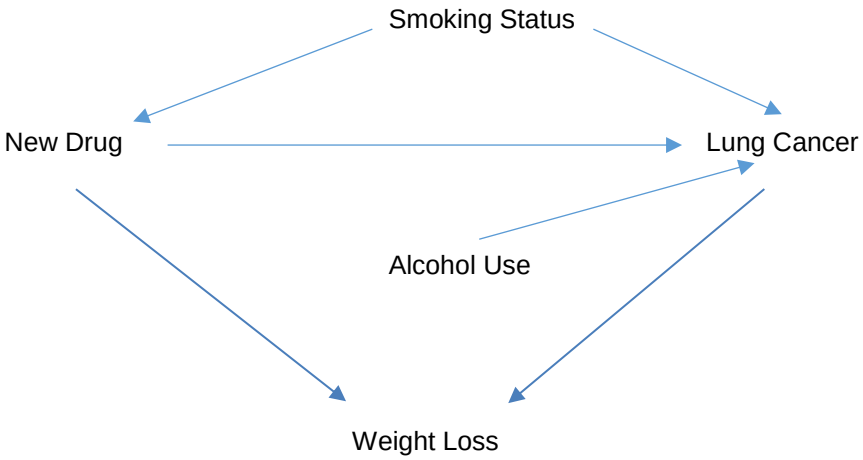


Figure 8.1 Example of a simple DAG (Direct Acyclic Graph) for a hypothetical study examining the relationship between a new drug and the risk of lung cancer

It is equally important to note the absence of an arrow from e.g. “Alcohol Use” to “New Drug” which indicates that the researcher believes that unlike with “Smoking Status”, “Alcohol Use” does not affect choice of “New Drug” but does affect the outcome being studied, “Lung Cancer”. Thus, such a variable would not confound results however, its inclusion may actually improve the precision of our desired final estimate of effect of “New Drug” on “Lung Cancer”.[165] In this example above, note that both the “New Drug” can lead to “weight loss” but also “Lung Cancer” itself can lead to “weight loss”. Here, “weight loss” is an example of a collider i.e. a common effect of both the exposure and outcome. This can be considered to be the opposite in many ways of a confounder. Such a variable should not be adjusted for as it can also introduce bias.[165]

The example in Figure 8.1 is simple for illustrative purposes, however, as one adds additional variables the models can increase considerably in complexity. The DAG allows the researcher to identify which variables may bias their study based on how they fit into the DAG and requires an intrinsically good knowledge of the clinical scenario underpinning their research question. Variables in a DAG, in summary, may affect exposure only, may affect outcome only, may affect both exposure and outcome and may affect other variables and by identifying all these relationships and their directionality, the subsequent study design and plan can become clearer.[164]

In Figure 8.2, I include the DAG I have generated for the cohort study that will be presented in Chapter 9 examining change in HbA1c from baseline comparing sitagliptin vs sulphonylureas as add-on to metformin. This DAG has been created using the online software DAGGITY®. This DAG highlights which variables I have identified that could confound my results (affect both exposure and outcome). My justification for inclusion of each of these variables is detailed in Table 8.1 below and have been agreed following discussion within a multidisciplinary team. It is evident from the DAG presented in Figure 8.2, that many of the variables that I plan to adjust for serve as proxies or surrogates for ascertaining how a clinician decides on choice of the exposure (sitagliptin or sulphonylureas). Equally, as no formal measure of adherence, diet or level of exercise is available in a primary care database, potential surrogates based on literature such as Townsend quintile (measure of social deprivation) are used.[166] This is of course, not ideal and a study limitation. Additionally, though ethnicity was identified as a possible theoretical confounder using the DAG, it is not well recorded in THIN and hence could not be used for the study.

Table 8.1 Justification for confounder selection for clinical model for analysis on HbA1c change

***A Priori* Confounders (measured at baseline)**	**Exposure Association**	**Outcome Association**
General		
Age at study entry	Imbalance at baseline - may affect treatment choice	Age may affect HbA1c control
Gender	Imbalance at baseline - may affect treatment choice	Gender may affect HbA1c control
Face to Face Consultation frequency (F2FC)	Imbalance at baseline - may affect treatment choice (for example sulphonylureas may increase hypoglycaemia risk therefore may be prescribed to an individual with better record of attendance to allow adequate monitoring)	Intensity of management as reflected in frequency of appointments may affect likelihood of HbA1c testing and thus control
Smoking Status	Imbalance at baseline – sulphonylureas may carry perceived higher cardiovascular risk - this may affect prescriber decision	Smoking can affect HbA1c control
Ethnicity*	Imbalance at baseline - may affect treatment choice as ethnic variation in treatment response to anti-diabetic has been reported	Ethnic variation in HbA1c control exists
Adherence**	History of poor medication adherence may affect prescriber choice of treatment	Poor medication adherence likely to worsen HbA1c control
Diet**	Type of diet at baseline may affect treatment choice –	Will affect HbA1c

***A Priori* Confounders (measured at baseline)**	**Exposure Association**	**Outcome Association**
	sulphonylureas carry higher risk of hypoglycaemias	
Exercise**	Level of exercise an individual undertakes may affect treatment choice	Will affect HbA1c
Year of add-on initiation	Will affect reasons for choice of exposure – guidance on choice of exposure has changed over time	Guidance on intensity of monitoring will affect frequency of measurements which could impact HbA1c control
Baseline HbA1c	Imbalance at baseline - may affect treatment choice	HbA1c change is outcome of interest
Baseline weight	Imbalance at baseline - may affect treatment choice. Sulphonylureas known to cause some weight gain	Will affect HbA1c control
Metformin dose (<1500mg or >1500mg)	Imbalance at baseline	Will affect HbA1c control
History of hypoglycaemias	Prescribers may favour sitagliptin where history of hypoglycaemia	Will affect HbA1c control
History of excessive alcohol use	Prescriber may avoid sulphonylureas as higher risk of hypoglycaemia with high alcohol intake	Will affect HbA1c control
Comorbidities		
Cancer	Imbalance at baseline - may affect treatment choice. Previous signals for sitagliptin and risk of pancreatic cancer have been raised.	Individuals with cancer may be more likely to have variable HbA1c control
Cardiovascular disease (CVD)	Imbalance at baseline - may affect treatment choice. sulphonylureas may be perceived to carry greater risk of future CVD events.	CVD may affect HbA1c control
Heart Failure (HF diagnosis or prescribed anti-HF med)	Imbalance at baseline - may affect treatment choice as conflicting signal with sitagliptin of worsening HF	HF indicative of poor CV health which may affect HbA1c control
Neuropathy	Imbalance at baseline - may affect treatment choice based on perceived diabetes severity and treatment efficacy	Marker of poor glycaemic control
Retinopathy	Imbalance at baseline - may affect treatment choice based on perceived diabetes severity and treatment efficacy	Marker of poor glycaemic control
Chronic Kidney Disease	Imbalance at baseline - may affect treatment choice. Dose reduction for sitagliptin needed in moderate to severe renal impairment	Likely to affect HbA1c control
Liver disease	Imbalance at baseline - may affect treatment choice.	Likely to affect HbA1c control

***A Priori* Confounders (measured at baseline)**	**Exposure Association**	**Outcome Association**
	Sitagliptin extensively hepatically metabolised	
Pancreatitis	If history of pancreatitis – prescriber may favour sulphonylureas (small increased risk of pancreatitis with sitagliptin has been reported)	History of pancreatic dysfunction may increase propensity for erratic glycaemic control
Arrythmias	Imbalance at baseline - may affect treatment choice as sulphonylureas may carry greater CVD risk	Marker of poor CV health which may affect HbA1c control
Medications		
Anti-hypertensive	Imbalance at baseline - may affect treatment choice e.g. Ramipril may not be prescribed for hypertension but be marker of CVD and hence affect treatment choice	Marker of poor CV health which may affect HbA1c control
Anti-arrythmics	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk. Not merged with arrythmia disease list as drugs only used in minority of arrythmias	Marker of poor CV health which may affect HbA1c control
Diuretics	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor CV health which may affect HbA1c control and diuretics known to affect glycaemic control directly as well
Antiplatelet	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor CV health which may affect HbA1c control
Anticoagulant	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor CV health which may affect HbA1c control
Antiobesity	Imbalance at baseline - may affect treatment choice as clinician may avoid sulphonylureas here to prevent excess weight gain	Will affect weight and in turn HbA1c control
Statins	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or a CVD risk	Poor CV health may affect HbA1c control while statins directly affect HbA1c control
Other lipid lowering drugs	Imbalance at baseline - may affect exposure choice	Poor CV health may affect HbA1c control while lipid lowering drugs may directly affect glycaemic control
Others		
Dementia	Imbalance at baseline - may affect exposure choice as sulphonylureas carry risk of hypoglycaemia	Dementia may act as a weak proxy for adherence to medication and hence glycaemic control
Townsend Quintile	Imbalance at baseline - may affect treatment choice	Those from higher Townsend Quintiles (more deprived) –

A Priori Confounders (measured at baseline)	Exposure Association	Outcome Association
		more likely to have diabetes and also may be potentially a weak proxy for worse adherence which would ultimately affect glycaemic control
Anxiolytics	History of anxiety may drive prescriber to avoiding sulphonylureas as carry greater risk of hypoglycaemia	May act as a weak proxy for adherence to medication and thus affect HbA1c
Antidepressants	History of depression may drive prescriber to avoiding sulphonylureas as carry greater risk of hypoglycaemia	May act as a weak proxy for adherence to medication and thus affect HbA1c

*Ethnicity though included in DAG was not well recorded in THIN.
**Diet, Adherence and Exercise not recorded in THIN hence proxies used where possible

Finally, several variables highlighted by blue shaded circles such as hypothyroidism in Figure 8.2, have been included as they are known to affect the outcome (HbA1c) though have not been deemed to affect treatment choice. Their inclusion is to improve model precision during analysis. In Table 8.2 below, I provide justification for including these variables.

Table 8.2 Justification for selection of variables associated with outcome for clinical model for analysis on HbA1c change

Variables measured at baseline which may affect outcome but not exposure	Exposure Association	Outcome Association
Comorbidities		
Hyperthyroidism	None	May affect metabolism and thereby HbA1c control
Hypothyroidism	None	May affect metabolism and thereby HbA1c control
Anaemias	None	Will affect oxygen carrying capacity of the blood, circulating red blood cells and in turn possibly HbA1c
Arrythmias	None	Marker of poor CV health which may affect HbA1c control
Medications		
Thyroxine	None	Will affect thyroid function and thus HbA1c control
Anti-thyroid drugs	None	Will affect thyroid function and thus HbA1c control
Antipsychotics	None	Several anti-psychotics directly affect HbA1c
Steroids – Oral/Intravenous	None	Will affect HbA1c control

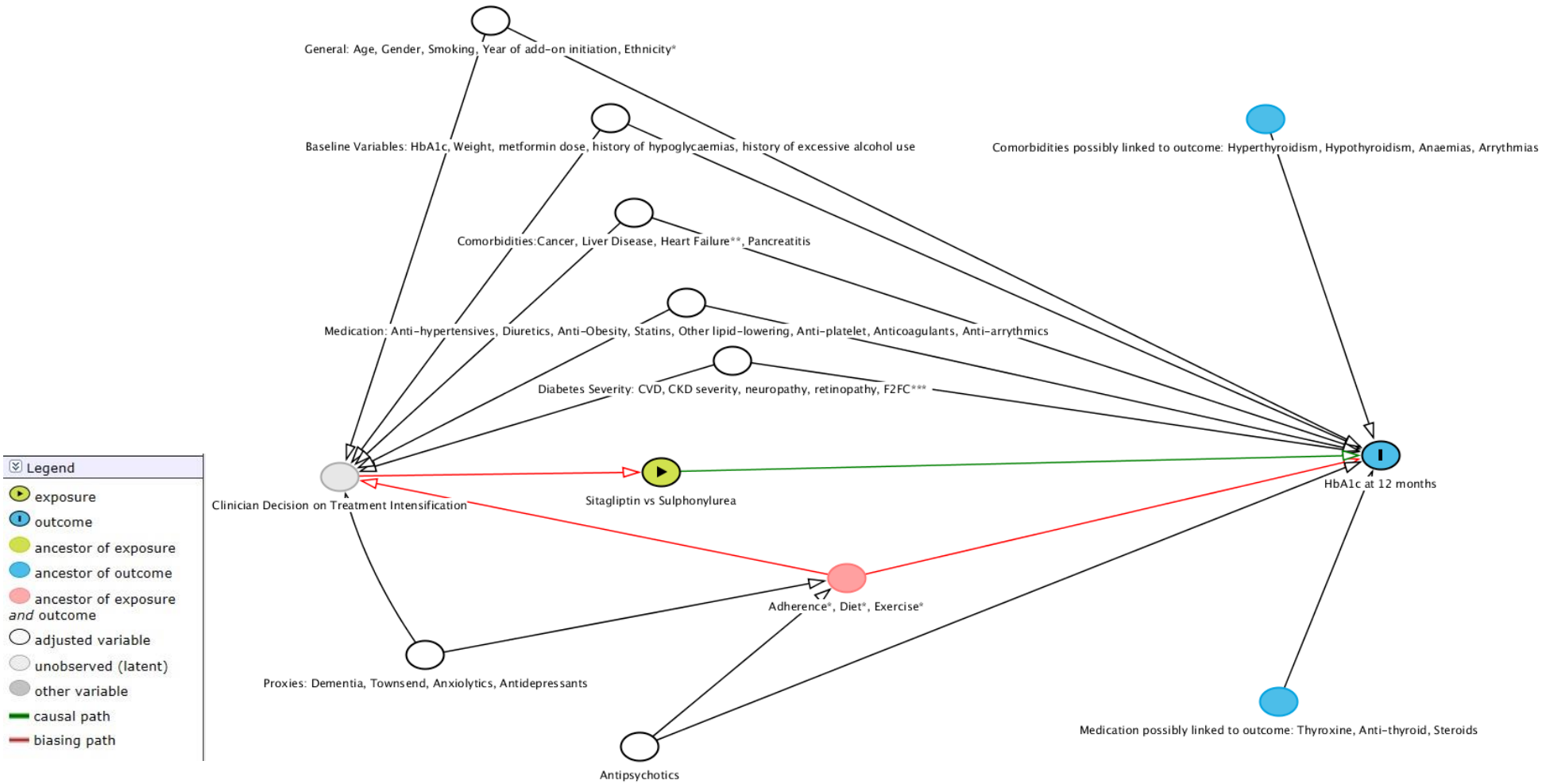


Figure 8.2 Direct Acyclic Graph depicting relationship between covariates, exposure and outcome for clinical model examining change in HbA1c approximately 12 months from baseline

*Ethnicity though included in DAG was not well recorded in THIN, Adherence, Diet and Exercise not recorded in THIN hence proxies used where possible
**Heart Failure refers to those with either Read code for Heart Failure recorded or on treatment
***Face to Face Consultation Frequency. CVD= Cardiovascular disease, CKD=Chronic Kidney Disease.

The DAG for the cohort study examining change in weight from baseline as well as the DAGs for analysis examining first recording of a HbA1c > 58 mmol/mol and treatment change will be presented in Chapters 9 and 10 respectively.

8.4 Propensity Score Matching

The traditional approach to handle confounding once identified, is through use of a regression model. Using a regression model, one can adjust for each confounding variable in turn, removing its effect and thus allowing estimation of unbiased estimates.

An alternative approach to remove the bias introduced through confounding variables involves matching the cohort study groups at baseline so as to produce two comparison groups that are more similar in their characteristics and distribution for the measured confounders (as well as other covariates that may be predictive of the outcome).[167] This matching can be undertaken through use of a propensity score. A propensity score is defined as an estimate of an individual's probability for receiving a treatment given the distribution of their measured covariate data.[168] Once calculated, the propensity score can be used as the sole criterion for matching individuals which is a major advantage, otherwise matching across individual component variables when the list of covariates is extensive can become mathematically impossible. A further advantage is that a perfect match is not required, and in fact one can be set by the researcher to a threshold deemed reasonable e.g. propensity scores within 0.05 distance of one another is a common threshold used for matching.[163] A comparison of baseline characteristics before and after propensity score matching also provides a useful means of assessing how successful the matching has been and potentially identifying factors which may bias results. Propensity score matching however, like any epidemiological analysis, cannot remove bias that may exist due to unmeasured confounding variables. In fact, a systematic review comparing results obtained by means of propensity score matching analysis and traditional regression analysis demonstrated that both approaches perform similarly.[169] There are several other methods for using the propensity score apart from matching, including adjustment and inverse probability weighting. Choosing a particular method for use of the propensity score can be somewhat arbitrary, with little evidence to suggest that any one method performs better than another.[170] As I am undertaking this analysis as a supportive analysis to my main regression analysis, I chose to use the propensity score matching method as it allows a useful assessment of covariate balance before and after matching. The alternate

methods for using the propensity score will not be discussed further as I will not use them in this thesis.[170,171]

8.5 Context of this chapter in overall work

This chapter emphasises the importance of identifying confounding variables in observational studies and controlling for them. I have summarised the use of Direct Acyclic Graphs as a method for identifying confounders as well as the use of propensity score matching for accounting for confounders in analysis. These methods will be employed in the cohort studies presented in the next chapters as supportive analysis alongside traditional regression analysis as well.

Chapter 9 Cohort studies examining change in HbA1c and change in weight from baseline

9.1 Chapter Overview

In this chapter, I will examine the comparative change in HbA1c and in weight from baseline (index date) for sitagliptin compared to sulphonylureas among individuals with type 2 diabetes mellitus (T2DM) as add-on to metformin. I will initially examine all individuals aged ≥ 18 years and then investigate whether there is any difference in effectiveness between those aged 18-75 years and older adults aged ≥ 75 years.

9.2 Rationale for study

The motivation for this analysis has been detailed in Chapter 3 (Section 3.2). Sitagliptin and sulphonylureas are the two most widely prescribed treatments as add-on to metformin for T2DM in the UK. "Real world" evidence is needed to determine the external validity of findings from previously undertaken randomised controlled trials investigating glycaemic and weight control with sitagliptin compared to sulphonylureas. There is also a paucity of evidence on the effectiveness of these medications in more comorbid as well as older individuals aged ≥ 75 years as they were largely excluded in the randomised trials. In this chapter, I will address these gaps in the evidence.

9.3 Study Objectives

1. To examine change in HbA1c approximately 12 months from baseline in individuals aged ≥ 18 years prescribed sitagliptin compared to sulphonylureas as add-on to metformin
2. To investigate whether changes in HbA1c observed in 1) differs in individuals aged ≥ 75 years compared to those aged 18-75 years
3. To examine change in weight approximately 12 months from baseline in individuals aged ≥ 18 years prescribed sitagliptin compared to sulphonylureas as add-on to metformin
4. To investigate whether changes in weight observed in 3) differs in individuals aged ≥ 75 years compared to those aged 18-75 years

9.4 Methods

9.4.1 Study Population

The cohort of individuals included in the analyses to follow and a summary of their demographic and clinical characteristics have been described in detail in Chapter 6 (Section 6.4.1). The full analysis cohort is comprised of individuals with T2DM who were issued at least one prescription for either sitagliptin or sulphonylureas as add-on to metformin between 2007 and 2014. Scientific approval to undertake this study was obtained from CMD Medical Research's Scientific Review Committee in August 2016. (SRC Reference Number: 16-072).

9.4.2 Statistical Analysis

I examined the difference in change in HbA1c and weight for those who initiated sitagliptin compared to those who initiated on sulphonylureas as add-on to metformin using regression analyses. For the final value of HbA1c or weight respectively, I used the earliest recorded value which was at least 9 and no more than 18 months after initiation of add-on treatment (see Chapter 7, Sections 7.4.2.1 and 7.4.2.2 for justification). For my analysis on HbA1c and weight, I presented 3 initial models; unadjusted analyses, analyses adjusted for baseline value (of HbA1c or weight respectively) and analyses adjusted for baseline value, sex and age. I also presented a fourth model, a fully adjusted parsimonious multivariable regression model adjusting for covariates shown to have significant association with treatment selection and both clinical outcomes in Chapters 6 and 7 respectively. Variables strongly associated with the outcomes were also included to help improve model precision.

I tested these models for evidence of effect modification by age via interactions between treatment and age group (among those older individuals aged ≥ 75 years vs those aged 18-75 years). [141] There was no evidence of effect modification by age group in the analysis for change in HbA1c. However this interaction was evident for the analysis on change in weight. Thus, I presented these latter results stratified by those aged 18-75 years and those aged ≥ 75 years. I also investigated whether there was evidence of clustering by practice in both the HbA1c and weight change analyses through the use of random effects models with a random intercept term included for each practice.[141] These models showed no evidence of significant practice effects for either outcome.

In addition to these models, I have presented additional supportive analysis (detailed below) for both HbA1c and weight change. These analyses served to further support my findings based on

use of parsimonious models for the analyses described above. The supportive analyses undertaken included:

1. Multivariable analyses adjusting for all covariates deemed to have a theoretical association with exposure (add-on treatment initiation) and outcome. This was referred to as the clinical model and the corresponding Direct Acyclic Graphs (DAGs) were also presented.
2. Propensity score matching analyses using all variables shown to have significant associations with the exposure and outcome in Chapters 6 and 7 was also presented. Matching was completed with a caliper size of 0.05. Standardised differences for continuous and binary variables and chi squared tests for categorical variables were presented before and after matching.
3. Subgroup analyses including only those individuals who were issued prescriptions for metformin and either sitagliptin or sulphonylureas (including combination pills) for at least 12 months (with no more than 60 days gap between successive prescriptions). This group was referred to as the "adherent" cohort with the caveat that this definition using issue of continuous prescriptions was only a surrogate measure for true adherence. That is, continuous prescribing is necessary, but not alone sufficient, for actual adherence to treatment.

9.5 Results

9.5.1 Cohort Size

Details of cohort sizes for the initial cohorts and for the cohorts with complete data to facilitate analyses for changes in HbA1c and weight are detailed in Table 9.1. The complete cohort consisted of those individuals with a recording for HbA1c or weight at baseline, as well as no missing recordings for other baseline covariates and at least 1 recorded HbA1c or weight value 9-18 months after the index date. Failure of this final inclusion criterion (missing outcome data recording between 9-18 months as shown in Section 9.5.4) led to the greatest reductions in cohort sizes for analyses.

Table 9.1 Cohort Sizes for analysis on HbA1c and weight change

Cohort		Total	Sitagliptin	Sulphonylureas
Full Population	Number of Individuals	**26,844**	4,630 (18%)	22,214 (82%)
	Aged≥ 75 years	3,324	407 (12%)	2,917 (88%)
	"Adherent" to Medications*	5,836	984 (17%)	4,852 (83%)
Complete Cohort for HbA1c**	Number of Individuals	**19,186**	3,306 (17%)	15,880 (83%)
	Aged≥ 75 years	2,305	266 (12%)	2,039 (88%)
	Adherent to Medications*	4,695	801 (17%)	3,894 (83%)
Complete Cohort for weight**	Number of Individuals	**18,023**	3,160 (18%)	14,863 (82%)
	Aged≥ 75 years	2,106	252 (12%)	1,854 (88%)
	"Adherent" to Medications*	4,406	764 (17%)	3,642 (83%)

*"Adherent" to both metformin and sitagliptin or sulphonylureas as defined by no greater than 60 day gap between successive prescriptions for 18 months.
**This is the number of individuals with a recording for final HbA1c or weight respectively, baseline HbA1c or weight respectively and other baseline covariates needed for analyses models.

9.5.2 Change in HbA1c from baseline

9.5.2.1 Flow diagram illustrating complete cohort size for analysis on HbA1c change

A detailed breakdown of how I arrived at the final complete cohort size of 19,186 individuals for the analysis on HbA1c change is presented in Figure 9.1. As can be seen, the main cause for loss of individuals (approximately 20%) was due to the absence of a recording of a final HbA1c value between 9-18 months after the index date.

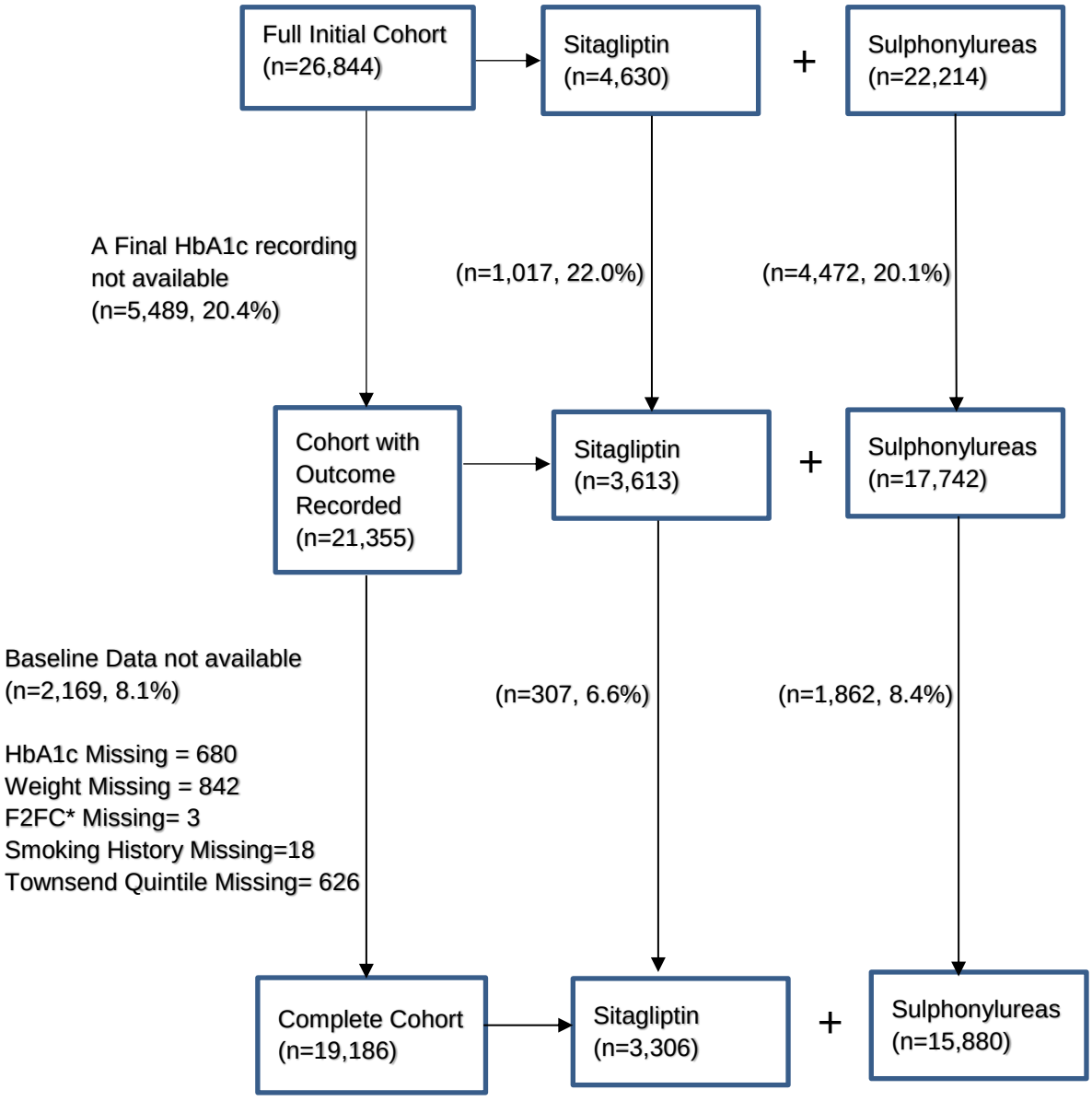


Figure 9.1 Flow diagram illustrating attrition from initial cohort to final complete cohort used for analysis for change in HbA1c

*Face to Face Consultation rate per year

Note: All percentage reductions in cohort size are calculated based on loss from full initial cohort

9.5.2.2 Baseline characteristics of complete cohort compared to cohort with missing outcome data and cohort missing baseline data (analysis on HbA1c change)

The baseline characteristics of all individuals initiated on sitagliptin vs sulphonylureas after metformin are detailed in Table 9.2 for the complete cohort (with no missing data) as well as the cohorts with missing outcome data and finally the cohort missing data for at least 1 baseline

covariate (i.e. missing at least 1 of: HbA1c, weight, Townsend quintiles, smoking or face to face consultation frequency). This summary of baseline characteristics indicates that the complete cohort and cohorts missing outcome data and some baseline data respectively were highly similar. The cohort missing some baseline data was however, considerably smaller in size (especially for those prescribed sitagliptin) more differences were apparent.

When compared to the complete cohort, a slightly higher baseline mean HbA1c was observed in sitagliptin and sulphonylurea cohorts that were missing outcome data and missing baseline data (i.e. 70.5 mmol/mol vs 73.7 mmol/mol vs 78.1 mmol/mol for sitagliptin and 74.5 mmol/mol vs 78.1 mmol/mol vs 79.9 mmol/mol for sulphonylureas respectively). The standard deviations across all these mean HbA1c values however, were in excess of 15 mmol/mol indicating considerable variability.

The percentage prescribed antiplatelets at baseline was also notably different in the complete cohort compared to cohorts that were missing outcome data and missing baseline data: 31.8% vs 27.8% vs 35.5% respectively for sitagliptin and 39.8% vs 32.7% vs 34.9% respectively for sulphonylureas. This also held true for statins prescribed at baseline: 79.8% vs 74.1% vs 76.5% respectively for sitagliptin and 78.3% vs 73.2% vs 69.5% respectively for sulphonylureas.

Table 9.2 Baseline characteristics of complete cohort, cohort missing outcome data and cohort missing some baseline data for analysis on HbA1c change

	Complete Cohort		**Missing Outcome Recording for HbA1c**		**Missing Some Baseline Covariate Data**	
	Sita	**Sulf**	**Sita**	**Sulf**	**Sita**	**Sulf**
Total (n)	**3306**	**15880**	**1017**	**4472**	**307**	**1862**
Baseline HbA1c mmol/mol, mean (SD)	70.5 (14.8)	74.5 (18.9)	73.7 (16.9)	78.1 (20.4)	78.1 (20.4)	79.9 (22.4)
Missing, n(%)	0 (0)	0 (0)	35 (3.4)	270 (6.0)	89 (29.0)	591 (31.7)
Age at index date years, mean (SD)	58.9 (11.2)	61.4 (11.7)	58.5 (12.3)	60.3 (12.9)	58.8 (12.8)	59.9 (13.1)
Sex						
Male	1976 (59.8)	9695 (61.1)	631 (62.0)	2796 (62.5)	162 (52.8)	1141 (61.3)
Female	1330 (40.2)	6185 (38.9)	386 (38.0)	1676 (37.5)	145 (47.2)	721 (38.7)
Baseline weight kg, mean (SD)	99.6 (21.9)	91.4 (19.7)	99.9 (22.5)	91.5 (20.6)	96 (23.4)	91.2 (20.6)
Missing, n(%)	0 (0)	0 (0)	60 (5.9)	417 (9.3)	122 (39.7)	854 (45.9)
Year Entry, n(%)						
2007	23 (0.7)	1866 (11.8)	7 (0.7)	288 (6.4)	3 (1.0)	220 (11.8)
2008	111 (3.4)	2446 (15.4)	13 (1.3)	472 (10.6)	16 (5.2)	296 (15.9)
2009	381 (11.5)	2878 (18.1)	62 (6.1)	530 (11.9)	24 (7.8)	303 (16.3)
2010	782 (23.7)	2629 (16.6)	114 (11.2)	481 (10.8)	79 (25.7)	277 (14.9)
2011	655 (19.8)	2242 (14.1)	130 (12.8)	455 (10.2)	70 (22.8)	282 (15.1)
2012	741 (22.4)	1967 (12.4)	139 (13.7)	513 (11.5)	57 (18.6)	255 (13.7)
2013	554 (16.8)	1677 (10.6)	194 (19.1)	667 (14.9)	53 (17.3)	206 (11.1)
2014	59 (1.8)	175 (1.1)	358 (35.2)	1066 (23.8)	5 (1.6)	23 (1.2)
F2FC*, mean (SD)	7.3 (5.0)	7.4 (5.0)	7.2 (6.1)	7 (5.1)	7.8 (6.4)	7.8 (5.5)

	Complete Cohort		Missing Outcome Recording for HbA1c		Missing Some Baseline Covariate Data	
	Sita	**Sulf**	**Sita**	**Sulf**	**Sita**	**Sulf**
Townsend Quintile, n(%)						
1 (least deprived)	802 (24.3)	3358 (21.1)	208 (20.5)	855 (19.1)	48 (15.6)	263 (14.1)
2	674 (20.4)	3373 (21.2)	195 (19.2)	864 (19.3)	32 (10.4)	251 (13.5)
3	802 (24.3)	3358 (21.1)	208 (20.5)	855 (19.1)	48 (15.6)	263 (14.1)
4	641 (19.4)	3215 (20.2)	218 (21.4)	977 (21.8)	43 (14.0)	271 (14.6)
5 (most deprived)	507 (15.3)	2510 (15.8)	132 (13.0)	687 (15.4)	33 (10.7)	190 (10.2)
Missing, n(%)	0 (0)	0 (0)	42 (4.1)	160 (3.6)	117 (38.1)	559 (30.0)
Smoker, n(%)						
Non	1569 (47.5)	7294 (45.9)	456 (44.8)	2050 (45.8)	148 (48.2)	832 (44.7)
Ex	1013 (30.6)	4902 (30.9)	312 (30.7)	1233 (27.6)	86 (28.0)	482 (25.9)
Current	724 (21.9)	3684 (23.2)	248 (24.4)	1181 (26.4)	71 (23.1)	524 (28.1)
CKD Stage, n(%)						
(CrCl>60 ml/min)	2946 (89.1)	13065 (82.3)	902 (88.7)	3736 (83.5)	265 (86.3)	1599 (85.9)
(CrCl 30-59 ml/min)	357 (10.8)	2775 (17.5)	115 (11.3)	718 (16.1)	42 (13.7)	261 (14.0)
(CrCl<30 ml/min)	3 (0.1)	40 (0.3)	0 (0)	18 (0.4)	0 (0)	2 (0.1)
Metformin Dose at Baseline, n(%)						
<1500mg	2595 (78.5)	12241 (77.1)	781 (76.8)	3320 (74.2)	215 (70.0)	1294 (69.5)
≥1500mg	711 (21.5)	3639 (22.9)	236 (23.2)	1152 (25.8)	92 (30.0)	568 (30.5)
Sulphonylurea Type, n(%)						
Gliclazide	-	14560 (91.7)	-	4161 (93.0)	-	1748 (93.9)
Glipizide	-	490 (3.1)	-	87 (1.9)	-	52 (2.8)
Glibenclamide	-	98 (0.6)	-	19 (0.4)	-	13 (0.7)
Tolbutamide	-	87 (0.5)	-	12 (0.3)	-	4 (0.2)
Glimepiride	-	1231 (7.8)	-	270 (6.0)	-	111 (6.0)
Chlorpropamide	-	0 (0)	-	0 (0)	-	0 (0)
Other	-	0 (0)	-	0 (0)	-	1 (0.1)
Binary Comorbidity Indicator Variables, n(%)						
Excessive Alcohol Intake**	507 (15.3)	2236 (14.1)	144 (14.2)	664 (14.8)	35 (11.4)	254 (13.6)
History of Hypoglycaemia	21 (0.6)	144 (0.9)	4 (0.4)	28 (0.6)	0 (0)	9 (0.5)
Neuropathy	107 (3.2)	643 (4.0)	35 (3.4)	176 (3.9)	15 (4.9)	75 (4.0)
Retinopathy	563 (17.0)	2234 (14.1)	153 (15.0)	574 (12.8)	31 (10.1)	172 (9.2)
Cardiovascular disease	840 (25.4)	4703 (29.6)	262 (25.8)	1271 (28.4)	79 (25.7)	559 (30.0)
Heart failure	337 (10.2)	1808 (11.4)	109 (10.7)	531 (11.9)	40 (13.0)	262 (14.1)
Anaemias	287 (8.7)	1366 (8.6)	82 (8.1)	393 (8.8)	36 (11.7)	168 (9.0)
Dementia	19 (0.6)	86 (0.5)	11 (1.1)	58 (1.3)	2 (0.7)	20 (1.1)
Liver disease	111 (3.4)	580 (3.7)	43 (4.2)	176 (3.9)	14 (4.6)	54 (2.9)
Arrythmias	222 (6.7)	1223 (7.7)	68 (6.7)	346 (7.7)	22 (7.2)	134 (7.2)
Cancer	435 (13.2)	2269 (14.3)	132 (13.0)	685 (15.3)	47 (15.3)	228 (12.2)
Hypothyroidism	261 (7.9)	1359 (8.6)	90 (8.8)	315 (7.0)	22 (7.2)	148 (7.9)
Hyperthyroid	36 (1.1)	238 (1.5)	13 (1.3)	56 (1.3)	4 (1.3)	21 (1.1)
Pancreatitis	35 (1.1)	217 (1.4)	11 (1.1)	78 (1.7)	3 (1.0)	38 (2.0)
Binary Treatment Indicator Variables¥, n(%)						
Anti-hypertensive	2299 (69.5)	11073 (69.7)	683 (67.2)	2968 (66.4)	206 (67.1)	1202 (64.6)
Antiplatelets	1051 (31.8)	6327 (39.8)	283 (27.8)	1462 (32.7)	109 (35.5)	650 (34.9)
Anticoagulants	148 (4.5)	723 (4.6)	48 (4.7)	192 (4.3)	8 (2.6)	77 (4.1)
Anti-arrythmic	17 (0.5)	111 (0.7)	4 (0.4)	24 (0.5)	1 (0.3)	15 (0.8)

	Complete Cohort		Missing Outcome Recording for HbA1c		Missing Some Baseline Covariate Data	
	Sita	**Sulf**	**Sita**	**Sulf**	**Sita**	**Sulf**
Diuretics	868 (26.3)	4351 (27.4)	237 (23.3)	1091 (24.4)	80 (26.1)	512 (27.5)
Statins	2639 (79.8)	12428 (78.3)	754 (74.1)	3274 (73.2)	235 (76.5)	1295 (69.5)
Other lipid lowering drugs	178 (5.4)	845 (5.3)	57 (5.6)	193 (4.3)	19 (6.2)	96 (5.2)
Antidepressants	593 (17.9)	2728 (17.2)	194 (19.1)	855 (19.1)	63 (20.5)	338 (18.2)
Antipsychotics	66 (2.0)	315 (2.0)	19 (1.9)	122 (2.7)	3 (1.0)	52 (2.8)
Antiobesity	91 (2.8)	210 (1.3)	14 (1.4)	47 (1.1)	6 (2.0)	18 (1.0)
Steroids – oral/intravenous	121 (3.7)	839 (5.3)	42 (4.1)	286 (6.4)	14 (4.6)	127 (6.8)
Thyroxine	249 (7.5)	1336 (8.4)	89 (8.8)	315 (7.0)	22 (7.2)	157 (8.4)
Anti-thyroid drugs	3 (0.1)	22 (0.1)	1 (0.1)	4 (0.1)	0 (0)	3 (0.2)
Anxiolytics	139 (4.2)	807 (5.1)	60 (5.9)	300 (6.7)	13 (4.2)	154 (8.3)

*Mean Face to Face Consultation Frequency per year
**Defined as recording of an intake of >35 units of alcohol a week for males or > 28 units for females
¥Concomitantly prescribed within 3 months prior to index date
CKD=Chronic Kidney Disease, CrCl=Creatinine Clearance estimated in ml/min, SD=Standard Deviation

9.5.2.3 Time of recording of baseline and final HbA1c

I selected the baseline HbA1c value recorded in the preceding 6 months that was closest to the index date. This definition also allowed for accepting a HbA1c recorded within 14 days after the index date as the baseline HbA1c as well. As evidenced from the histogram in Figure 9.2, the majority of baseline values for individuals were clustered close to the index date.

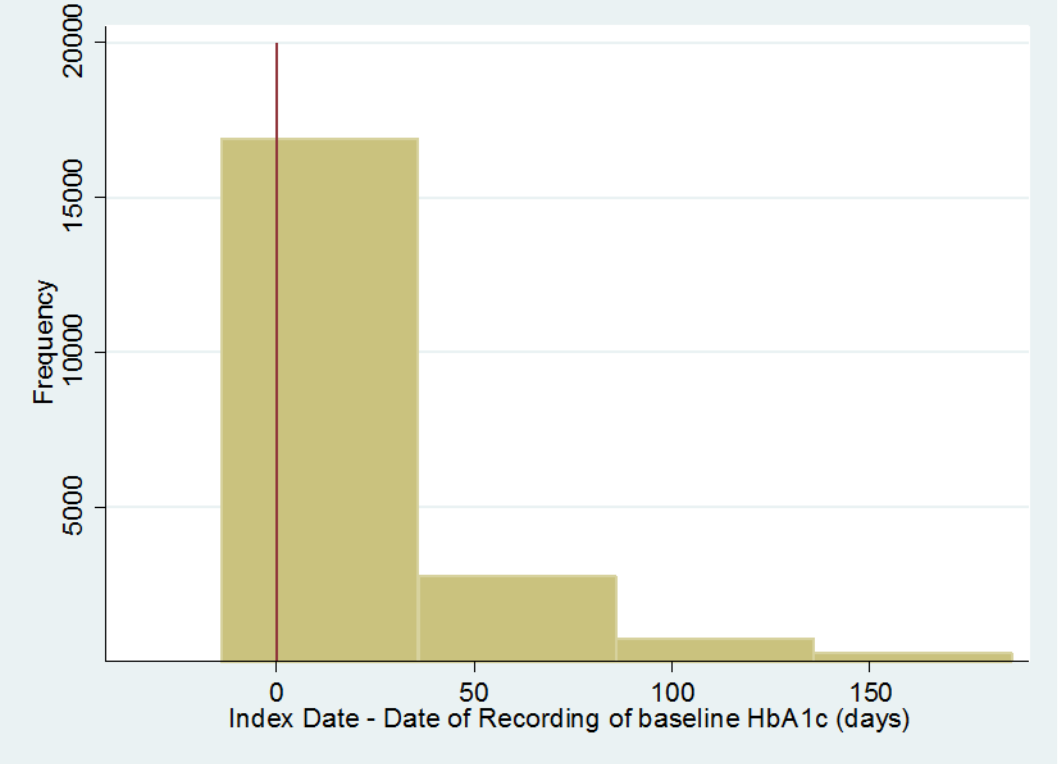


Figure 9.2 Histogram displaying frequency of recording of baseline HbA1c relative to index date (date on which sitagliptin or sulphonylureas prescription was initiated)
*Note that several HbA1c baseline recordings are recorded after the index date. This is because a HbA1c recorded within 14 days after the index date was also accepted as a baseline HbA1c recording (see Chapter 6, Section 6.3.1)

However, there were outliers for whom the baseline HbA1c had in fact been recorded as far back as 150-180 days before the index date. Similarly, the final HbA1c was recorded largely within +/- 90 days of 12 months (365 days) after the index date as shown in the distribution in Figure 9.3

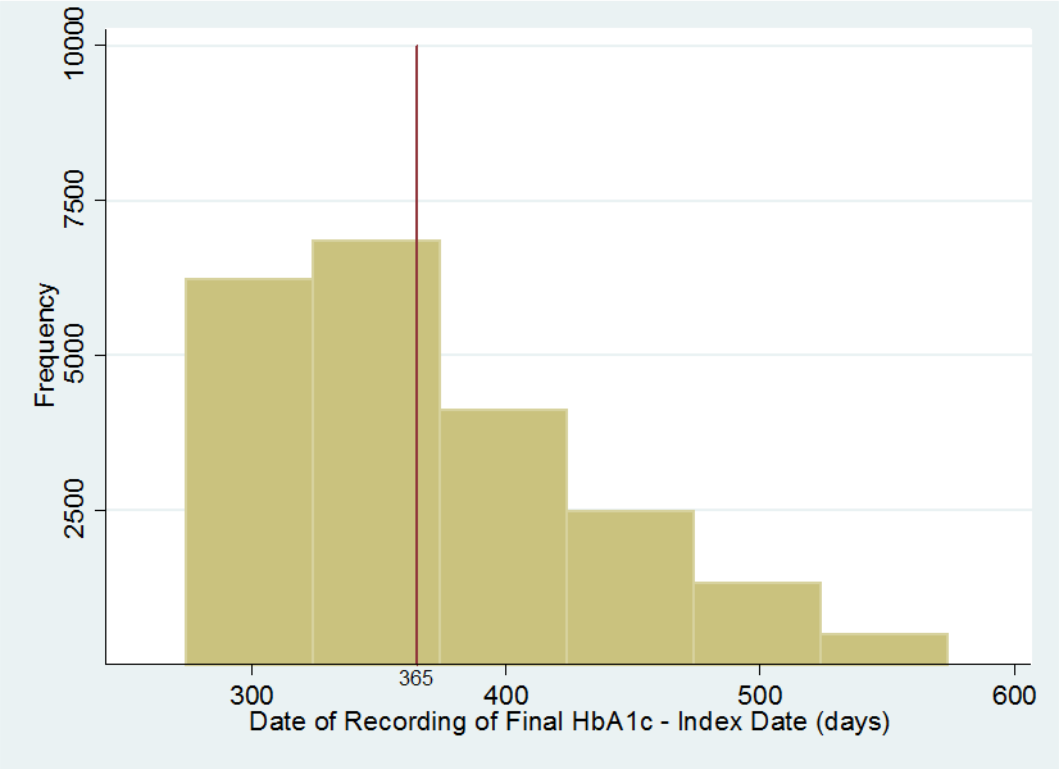


Figure 9.3 Histogram displaying distribution of time of recording of final HbA1c relative to 365 days (1 year) after index date (date on which sitagliptin or sulphonylurea prescription was initiated)

9.5.2.4 Population level mean HbA1c at 3 monthly intervals after the index date

The population level mean HbA1c (for all individuals with valid HbA1c measurements within each respective 3 monthly interval) after the index date for initiation of either sitagliptin or sulphonylureas is illustrated in Figure 9.4. A more rapid decline in mean HbA1c was evident with sulphonylureas within the first 6 months compared to sitagliptin, however this rapid decline levelled out thereafter.

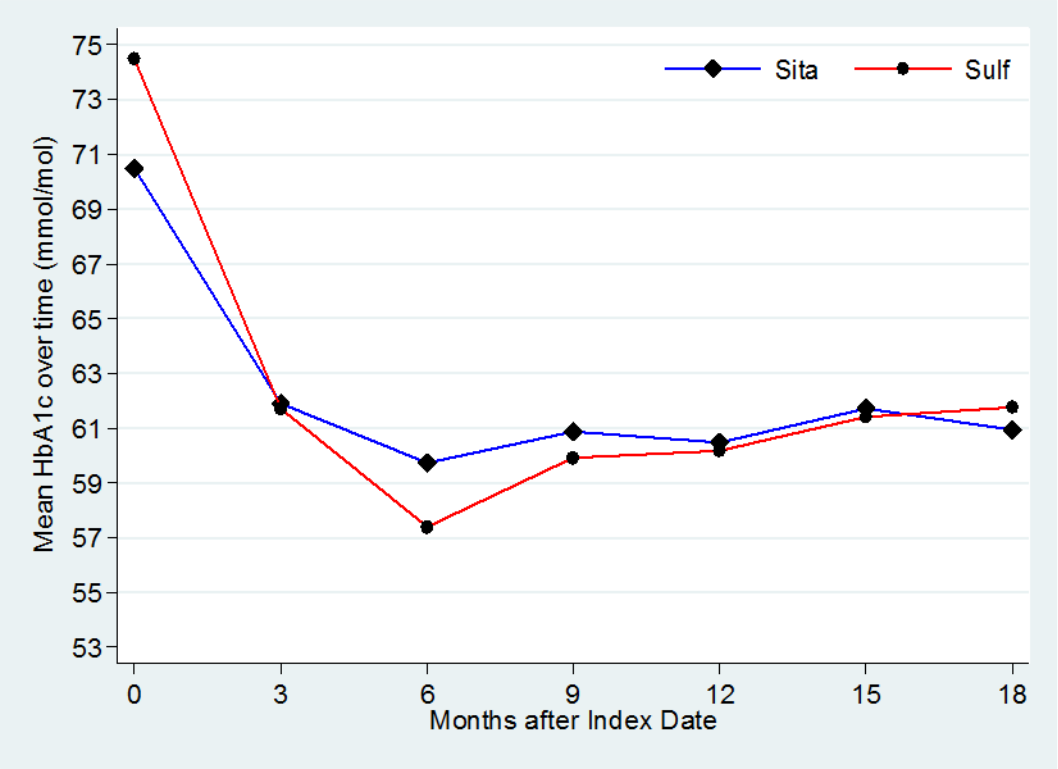


Figure 9.4 Mean HbA1c (mmol/mol) recorded over time
*Mean calculated based on all individuals with valid HbA1c measurements for each respective 3 monthly interval

9.5.2.5 Main analysis

At baseline, individuals prescribed sitagliptin had a mean HbA1c of 70.5 mmol/mol. However approximately 12 months after baseline, the mean HbA1c reduced to 60.9 mmol/mol [paired t-test: mean reduction -9.6 mmol/mol (95% CI -9.0 to -10.2)]. For individuals prescribed sulphonylureas, the mean HbA1c was 74.5 mmol/mol at treatment initiation and reduced to 60.4 mmol/mol after approximately 12 months [paired t-test: mean reduction -14.2 mmol/mol (95% CI -13.9 to -14.5)].

After adjustment for baseline HbA1c, sex, age and other baseline covariates identified for inclusion in the parsimonious regression model, the HbA1c approximately 12 months after the index date was on average 0.89 mmol/mol (95% CI 0.33 to 1.45) higher for those prescribed sitagliptin compared to sulphonylureas, (Table 9.3).

Therefore, though both treatments reduced HbA1c from baseline, a smaller comparative reduction was observed with sitagliptin of on average 0.89 mmol/mol in magnitude, having accounted for baseline differences.

The results for the clinical model (after adjustment for all covariates considered theoretically to confound results) did not differ from the analysis using the parsimonious model. The Direct Acyclic Graph (Figure 9.5) details the confounders included in this analysis model. The justification for their selection was provided earlier in Chapter 8 (Section 8.3, Tables 8.1 and 8.2).

In the cohort of individuals who met the definition of "adherent" to the respective treatments, the HbA1c approximately 12 months after the index date was on average -1.01 mmol/mol (-1.86 to -0.16) lower for those prescribed sitagliptin compared to sulphonylureas, (Table 9.3). This suggested that in this subgroup, the comparative reduction observed with sitagliptin was on average 1.01 mmol/mol greater in magnitude than sulphonylureas, having accounted for baseline differences.

The full output for all three analyses is summarised in Table 9.3 below and is included in full in Appendix F (Supplementary Tables 9A1-9A3) for reference.

Table 9.3 Regression Analysis for mean difference in HbA1c (mmol/mol) approximately 12 months after baseline for adults aged ≥ 18 years

Model: Sitagliptin vs Sulphonylureas	**Unadjusted, mean diff (95% CI)**	**Adjusted for baseline, HbA1c, mean diff (95% CI)**	**Adjusted for Sex, Age & Baseline HbA1c, mean diff (95% CI)**	**Fully Adjusted Multivariable¥, mean diff (95% CI)**
Aged ≥ 18 years				
Parsimonious model (n=19,186)	0.55 (-0.04 to 1.13)	1.78 (1.23 to 2.33)	1.13 (0.59 to 1.67)	0.89 (0.33 to 1.45)
Clinical model (n=19,186)	(as above)	(as above)	(as above)	0.88 (0.32 to 1.45)
"Adherent" population (n=4,695)	-0.89 (-1.76 to -0.02)	0.27 (-0.56 to 1.10)	-0.13 (-0.95 to 0.70)	-1.01 (-1.86 to -0.16)

¥Mutually adjusted for baseline HbA1c, baseline weight, age, year entry, F2FC (Average Face to Face consultation frequency per year), sex, Townsend quintile, smoking status, metformin dose, history of excessive alcohol intake, hypoglycaemia, neuropathy, heart failure, anaemias, liver disease and having a prescription within 3 months prior to the index date for diuretics, statins, antidepressants and oral or intravenous steroid medication.
Mean diff=mean difference, CI=confidence interval.
Note: Individuals prescribed sulphonylureas are the reference population in all regression estimates above.

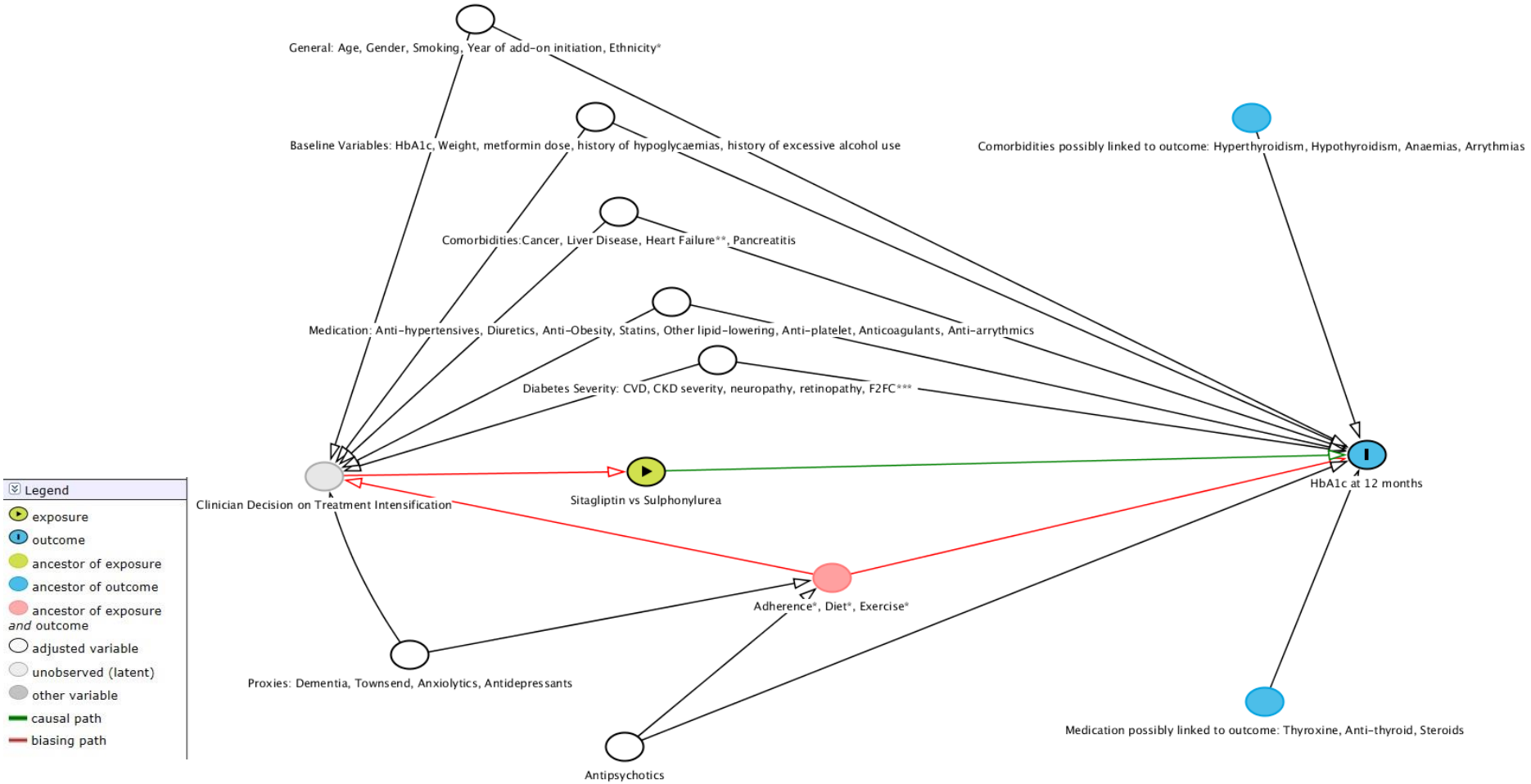


Figure 9.5 Direct Acyclic Graph depicting relationship between covariates, exposure and outcome for clinical model examining change in HbA1c approximately 12 months from baseline

*Ethnicity though included in DAG was not well recorded in THIN, Adherence, Diet and Exercise not recorded in THIN hence proxies used where possible

**Heart Failure refers to those with either read code for Heart Failure recorded or on treatment for Heart Failure.

***Face to Face Consultation Frequency

CVD= Cardiovascular disease; CKD=Chronic Kidney Disease

9.5.2.6 Propensity Score Matching Analysis

The propensity for being prescribed sitagliptin is displayed in Figure 9.6 (previously displayed in Chapter 6, Section 6.4.5) and highlighted that the sitagliptin and sulphonylurea cohorts differed across a range of measured covariates at baseline. However, there was overlap between the two curves in Figure 9.6 which indicated there were individuals within the sitagliptin and sulphonylurea groups (based on a distribution of their measured covariates) who may have had similar propensity to be prescribed sitagliptin or sulphonylureas.

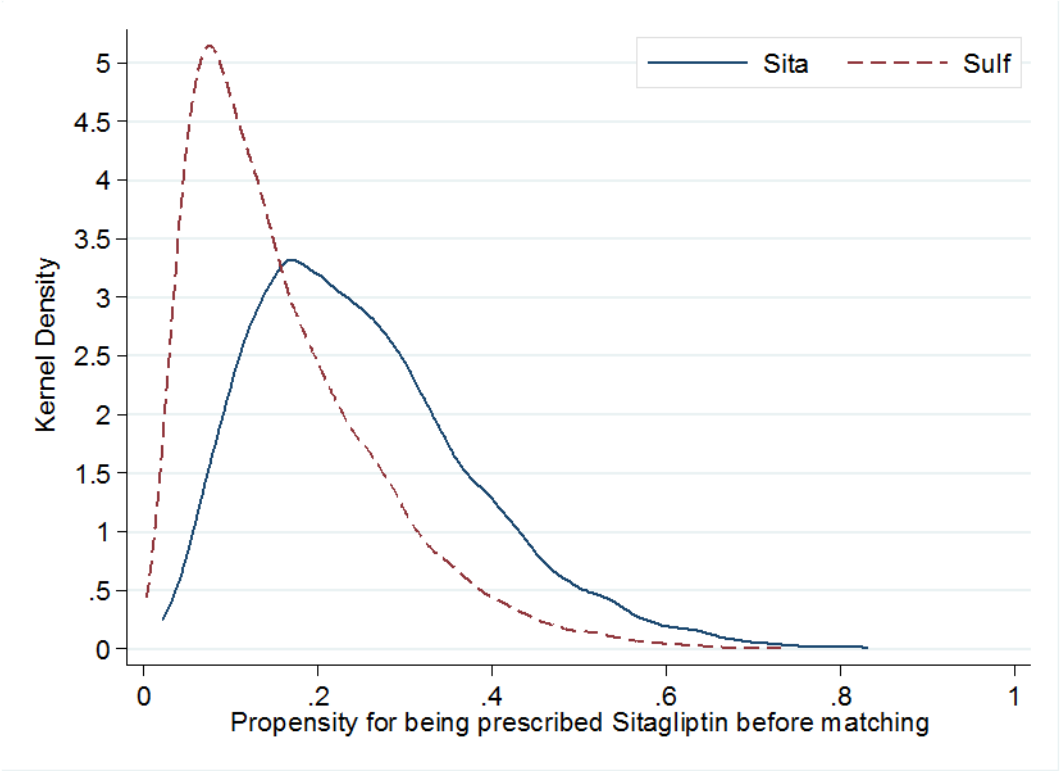


Figure 9.6 Kernel density plot of propensity for being prescribed sitagliptin based on distribution of measured characteristics at baseline for both individuals prescribed sitagliptin and sulphonylureas before matching
Note: A logistic regression analysis was used to produce this plot, details of the full regression analysis and output can be found in Appendix D (Supplementary Figure 6A4).

Propensity score matching was highly successful as evidenced in Table 9.4, where I present the standardised differences and chi-squared tests before and after matching the cohort. For example, baseline HbA1c which was markedly different before matching showed no significant difference after matching (70.5 mmol/mmol and 74.5 mmol/mol before matching and 70.5 mmol/mol and 70.7 mmol/mol after matching for sitagliptin and sulphonylureas respectively). Additionally, variables such as weight, Townsend quintiles as well as comorbidities and prescribed medication which were also significantly different prior to matching, were no longer different after matching.

Table 9.4 Standardised Differences and Chi-squared tests before and after propensity-score matching for analysis on HbA1c change

	Pre-matching				Post-matching			
	Sita	**Sulf**	**Stand Diff**	**P-value**	**Sita**	**Sulf**	**Stand Diff**	**P-value**
Total	**3306**	**15880**			**3306**	**3306**		
Baseline HbA1c mmol/mol, mean (SD)	70.5 (14.8)	74.5 (18.9)	-0.236	**<0.001**	70.5 (14.8)	70.7 (15.5)	-0.012	0.639
Age at index date, mean (SD)	58.9 (11.2)	61.4 (11.7)	-0.217	**<0.001**	58.9 (11.2)	58.8 (11.6)	0.005	0.838
Sex, n(%)								
Male	1976 (59.8)	9695 (61.1)	-0.026	0.170	1976 (59.8)	2005 (60.6)	-0.018	0.466
Female	1330 (40.2)	6185 (38.9)			1330 (40.2)	1301 (39.4)		
Baseline weight kg, mean (SD)	99.6 (21.9)	91.4 (19.7)	0.393	**<0.001**	99.6 (21.9)	99.5 (22.8)	0.004	0.859
Year Entry, n (%)				**<0.001***				0.865*
2007	23 (0.7)	1866 (11.8)			23 (0.7)	29 (0.9)		
2008	111 (3.4)	2446 (15.4)			111 (3.4)	103 (3.1)		
2009	381 (11.5)	2878 (18.1)			381 (11.5)	351 (10.6)		
2010	782 (23.7)	2629 (16.6)			782 (23.7)	808 (24.4)		
2011	655 (19.8)	2242 (14.1)			655 (19.8)	645 (19.5)		
2012	741 (22.4)	1967 (12.4)			741 (22.4)	735 (22.2)		
2013	554 (16.8)	1677 (10.6)			554 (16.8)	571 (17.3)		
2014	59 (1.8)	175 (1.1)			59 (1.8)	64 (1.9)		
F2FC**, mean(SD)	7.3 (5.0)	7.4 (5.0)	-0.036	0.062	7.3 (5.0)	7.3 (5.1)	-0.011	0.644
Townsend Quintile, n(%)				**0.003***				0.867*
1 (least deprived)	802 (24.3)	3358 (21.1)			802 (24.3)	766 (23.2)		
2	674 (20.4)	3373 (21.2)			674 (20.4)	675 (20.4)		
3	802 (24.3)	3358 (21.1)			802 (24.3)	766 (23.2)		
4	641 (19.4)	3215 (20.2)			641 (19.4)	646 (19.5)		
5 (most deprived)	507 (15.3)	2510 (15.8)			507 (15.3)	525 (15.9)		
Smoker, n(%)				0.179*				0.923*
Non	1569 (47.5)	7294 (45.9)			1569 (47.5)	1574 (47.6)		
Ex	1013 (30.6)	4902 (30.9)			1013 (30.6)	999 (30.2)		
Current	724 (21.9)	3684 (23.2)			724 (21.9)	733 (22.2)		
Metformin Dose at Baseline, n(%)								
<1500mg	2595 (78.5)	12241 (77.1)	-0.034	0.078	2595 (78.5)	2601 (78.7)	0.004	0.857
≥1500mg	711 (21.5)	3639 (22.9)			711 (21.5)	705 (21.3)		
Binary Comorbidity Indicator Variables, n(%)								
Excessive alcohol intake †	507 (15.3)	2236 (14.1)	-0.035	0.061	507 (15.3)	511 (15.5)	0.003	0.892
History of Hypoglycaemia	21 (0.6)	144 (0.9)	0.031	0.124	21 (0.6)	18 (0.5)	-0.012	0.630
Neuropathy	107 (3.2)	643 (4.0)	0.043	**0.028**	107 (3.2)	113 (3.4)	0.010	0.681
Heart failure	337 (10.2)	1808 (11.4)	0.038	**0.048**	337 (10.2)	340 (10.3)	0.003	0.903
Anaemias	287 (8.7)	1366 (8.6)	-0.003	0.883	287 (8.7)	284 (8.6)	-0.003	0.896
Liver disease	111 (3.4)	580 (3.7)	0.016	0.408	111 (3.4)	110 (3.3)	-0.002	0.945

	Pre-matching				Post-matching			
Binary Treatment Indicator Variables¥, n(%)								
Diuretics	868 (26.3)	4351 (27.4)	0.026	0.179	868 (26.3)	879 (26.6)	0.008	0.759
Statins	2639 (79.8)	12428 (78.3)	-0.038	**0.047**	2639 (79.8)	2645 (80.0)	0.005	0.854
Antidepressants	593 (17.9)	2728 (17.2)	-0.020	0.294	593 (17.9)	594 (18.0)	0.001	0.974
Steroids – oral/intravenous	121 (3.7)	839 (5.3)	0.079	**<0.001**	121 (3.7)	135 (4.1)	0.022	0.372

*P-value derived from chi squared test.
**Mean Face to Face Consultation Frequency per year
†Excessive alcohol intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months prior to index date.
Sita=Sitagliptin, Sulf=Sulphonylurea, SD=Standard Deviation, Stand Diff=standardised difference.
Note: P-values in bold are statistically significant at <0.05 level.

Further evidence of successful matching is also provided in Figure 9.7 where nearly complete overlap of both sitagliptin and sulphonylureas curves after matching, confirms a similar distribution of measured covariates across both groups.

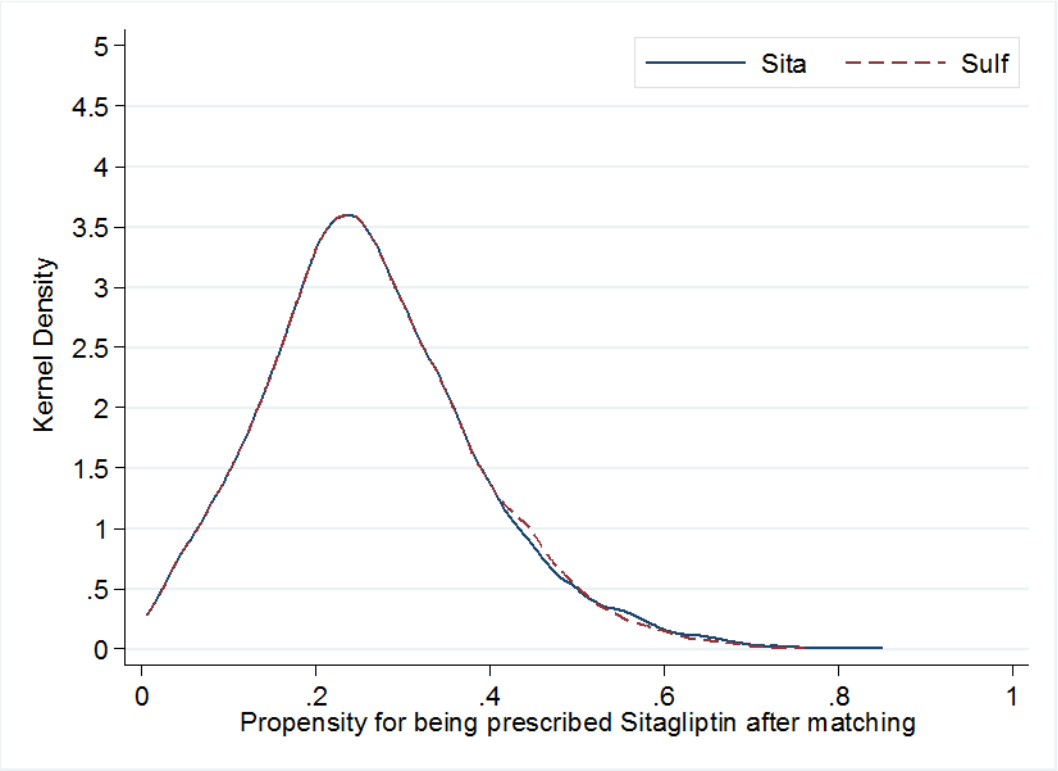


Figure 9.7 Kernel density plot of propensity for being prescribed sitagliptin based on distribution of measured characteristics at baseline for both individuals prescribed sitagliptin and sulphonylureas after matching (analysis on HbA1c change)

The Average Treatment Effect estimated for this cohort of 3,306 matched pairs was 0.83 mmol/mol (95% CI 0.04 to 1.60) and was a similar estimate to that observed with the main regression analyses. This also suggested a smaller comparative reduction in HbA1c was observed with sitagliptin of on average 0.83 mmol/mol in magnitude, after matching.

9.5.3 Change in weight from baseline

9.5.3.1 Flow diagram illustrating complete cohort size for analysis on HbA1c change

A detailed breakdown of how I arrived at the final complete cohort size of 18,023 individuals for the analysis on weight change is presented in Figure 9.8. As can be seen, the main cause for loss of individuals (approximately 28%) was due to the absence of a recording for a final weight value 9-18 months after the index date.

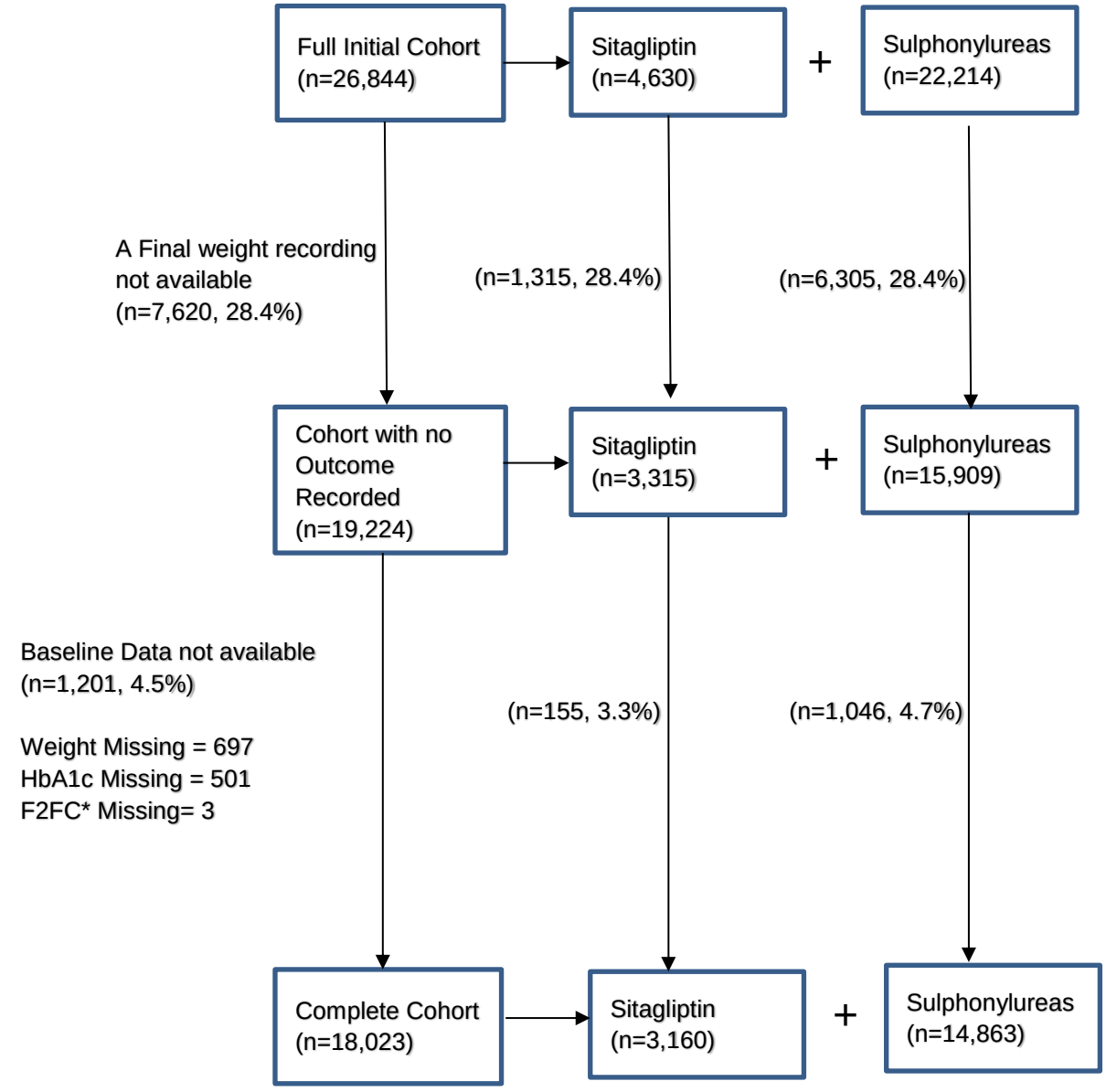


Figure 9.8 Flow diagram illustrating attrition from initial cohort to final complete cohort used for analysis for change in weight

*Face to Face Consultation frequency per year

Note: All percentage reductions in cohort size are calculated based on loss from full initial cohort

9.5.3.2 Baseline characteristics of complete cohort compared to cohort with missing outcome and cohort missing baseline data (analysis on weight change)

The baseline characteristics of all individuals initiated on sitagliptin vs sulphonylureas after metformin are detailed in Table 9.5 for the complete cohort (with no missing data) as well as the cohorts with missing outcome data and the cohort missing data for at least 1 baseline covariate (i.e. missing at least 1 of: weight, HbA1c, Townsend quintiles, smoking or face to face consultation frequency). This summary of an extensive set of baseline characteristics highlights that the complete cohort and cohort missing outcome data were highly similar across the majority of covariates. However, as the cohort missing baseline data was considerably smaller in size especially for sitagliptin more differences were apparent.

When compared to the complete cohort, the baseline mean HbA1c among sitagliptin and sulphonylurea groups in the cohort missing outcome data and cohort missing some baseline data were different (70.4 mmol/mol vs 73.6 mmol/mol vs 77.9 mmol/mol for sitagliptin and 74.4 mmol/mol vs 77.9 mmol/mol vs 82.8 mmol/mol for sulphonylureas respectively). The standard deviations across all these mean HbA1c values however, were in excess of 14 mmol/mol indicating considerable variability and overlap in distributions.

The percentage with a history of retinopathy across the three cohorts were (16.8% vs 15.7% vs 6.5% respectively for sitagliptin and 14.0% vs 12.9% vs 8.2% respectively for sulphonylureas), and for statins prescribed at baseline, the percentages were (79.1% vs 76.7% vs 77.4% respectively for sitagliptin and 78.3 % vs 74.3% vs 65.1% respectively for sulphonylureas).

Table 9.5 Baseline characteristics of complete cohort, cohort missing outcome data and cohort missing some baseline data for analysis on weight change

	Complete Cohort		Missing Outcome Recording for Weight		Missing Some Baseline Covariate Data	
	Sita	**Sulf**	**Sita**	**Sulf**	**Sita**	**Sulf**
Total (n)	**3160**	**14863**	**1315**	**6305**	**155**	**1046**
Baseline HbA1c mmol/mol, mean (SD)	70.4 (14.7)	74.4 (18.9)	73.6 (17.0)	77.9 (20.5)	77.9 (20.5)	82.8 (23.2)
Missing, n(%)	0 (0)	0 (0)	45 (3.4)	332 (5.3)	79 (51.0)	529 (50.6)
Age at index date	58.8 (11.2)	61.2 (11.7)	58.8 (12.2)	60.8 (12.8)	59.1 (12.7)	59.5 (12.9)
Sex						
Male	1871 (59.2)	9113 (61.3)	818 (62.2)	3878 (61.5)	80 (51.6)	641 (61.3)
Female	1289 (40.8)	5750 (38.7)	497 (37.8)	2427 (38.5)	75 (48.4)	405 (38.7)
Baseline weight kg, mean (SD)	99.5 (21.8)	91.5 (19.6)	99.6 (22.6)	91.1 (20.6)	95.8 (24.4)	91.4 (21.3)
Missing, n(%)	0 (0)	0 (0)	92 (7.0)	664 (10.5)	90 (58.1)	607 (58.0)
Year Entry, n(%)						
2007	25 (0.8)	1775 (11.9)	6 (0.5)	476 (7.5)	2 (1.3)	123 (11.8)
2008	110 (3.5)	2369 (15.9)	21 (1.6)	674 (10.7)	9 (5.8)	171 (16.3)

	Complete Cohort		Missing Outcome Recording for Weight		Missing Some Baseline Covariate Data	
	Sita	**Sulf**	**Sita**	**Sulf**	**Sita**	**Sulf**
2009	359 (11.6)	2697 (18.1)	98 (7.5)	832 (13.2)	10 (6.5)	182 (17.4)
2010	757 (24.4)	2467 (16.6)	177 (13.5)	755 (12.0)	41 (26.5)	165 (15.8)
2011	648 (20.9)	2145 (14.4)	167 (12.7)	671 (10.6)	40 (25.8)	163 (15.6)
2012	697 (22.4)	1804 (12.1)	212 (16.1)	803 (12.7)	28 (18.1)	128 (12.2)
2013	511 (16.5)	1466 (9.9)	269 (20.5)	978 (15.5)	21 (13.5)	106 (10.1)
2014	53 (1.7)	140 (0.9)	365 (27.8)	1116 (17.7)	4 (2.6)	8 (0.8)
F2FC*, mean (SD)	7.3 (5.1)	7.5 (5.0)	7.1 (5.6)	7.1 (5.1)	7.9 (7.0)	7.6 (5.3)
Townsend Quintile, n(%)						
1 (least deprived)	728 (23.0)	3019 (20.3)	297 (22.6)	1253 (19.9)	33 (21.3)	204 (19.5)
2	620 (19.6)	3091 (20.8)	256 (19.5)	1202 (19.1)	25 (16.1)	195 (18.6)
3	728 (23.0)	3019 (20.3)	297 (22.6)	1253 (19.9)	33 (21.3)	204 (19.5)
4	602 (19.1)	2935 (19.7)	262 (19.9)	1330 (21.1)	38 (24.5)	198 (18.9)
5 (most deprived)	459 (14.5)	2257 (15.2)	188 (14.3)	974 (15.4)	25 (16.1)	156 (14.9)
Missing, n(%)	105 (3.3)	473 (3.2)	49 (3.7)	208 (3.3)	5 (3.2)	38 (3.6)
Smoking Status, n(%)						
Non	1470 (46.5)	6794 (45.7)	635 (48.3)	2913 (46.2)	68 (43.9)	469 (44.8)
Ex	978 (30.9)	4592 (30.9)	392 (29.8)	1740 (27.6)	41 (26.5)	285 (27.2)
Current	711 (22.5)	3462 (23.3)	286 (21.7)	1642 (26.0)	46 (29.7)	285 (27.2)
CKD Stage, n(%)						
(CrCl>60 ml/min)	2817 (89.1)	12248 (82.4)	1160 (88.2)	5251 (83.3)	136 (87.7)	901 (86.1)
(CrCl 30-59 ml/min)	342 (10.8)	2579 (17.4)	153 (11.6)	1031 (16.4)	19 (12.3)	144 (13.8)
(CrCl<30 ml/min)	1 (0.0)	36 (0.2)	2 (0.2)	23 (0.4)	0 (0)	1 (0.1)
Metformin Dose at Baseline, n(%)						
<1500mg	2468 (78.1)	11473 (77.2)	1025 (77.9)	4692 (74.4)	98 (63.2)	690 (66.0)
≥1500mg	692 (21.9)	3390 (22.8)	290 (22.1)	1613 (25.6)	57 (36.8)	356 (34.0)
Sulphonylurea Type, n(%)						
Gliclazide	-	13592 (91.4)	-	5893 (93.5)	-	984 (94.1)
Glipizide	-	483 (3.2)	-	123 (2.0)	-	23 (2.2)
Glibenclamide	-	87 (0.6)	-	33 (0.5)	-	10 (1.0)
Tolbutamide	-	79 (0.5)	-	20 (0.3)	-	4 (0.4)
Glimepiride	-	1178 (7.9)	-	372 (5.9)	-	62 (5.9)
Chlorpropamide	-	0 (0)	-	0 (0)	-	0 (0)
Other	-	0 (0)	-	0 (0)	-	1 (0.1)
Binary Comorbidity Indicator Variables, n(%)						
Heavydrinker**	490 (15.5)	2111 (14.2)	179 (13.6)	902 (14.3)	17 (11.0)	141 (13.5)
History of Hypoglycaemia	20 (0.6)	134 (0.9)	5 (0.4)	43 (0.7)	0 (0)	4 (0.4)
Neuropathy	107 (3.4)	595 (4.0)	41 (3.1)	261 (4.1)	9 (5.8)	38 (3.6)
Retinopathy	531 (16.8)	2081 (14.0)	206 (15.7)	813 (12.9)	10 (6.5)	86 (8.2)
Cardiovascular disease	808 (25.6)	4418 (29.7)	335 (25.5)	1806 (28.6)	38 (24.5)	309 (29.5)
Heart failure	328 (10.4)	1673 (11.3)	136 (10.3)	797 (12.6)	22 (14.2)	131 (12.5)
Anaemias	288 (9.1)	1252 (8.4)	105 (8.0)	569 (9.0)	12 (7.7)	106 (10.1)
Dementia	17 (0.5)	68 (0.5)	13 (1.0)	85 (1.3)	2 (1.3)	11 (1.1)
Liver disease	107 (3.4)	540 (3.6)	55 (4.2)	245 (3.9)	6 (3.9)	25 (2.4)
Arrythmias	212 (6.7)	1125 (7.6)	88 (6.7)	508 (8.1)	12 (7.7)	70 (6.7)
Cancer	408 (12.9)	2108 (14.2)	183 (13.9)	945 (15.0)	23 (14.8)	129 (12.3)
Hypothyroidism	249 (7.9)	1238 (8.3)	109 (8.3)	512 (8.1)	15 (9.7)	72 (6.9)
Hyperthyroid	37 (1.2)	209 (1.4)	13 (1.0)	95 (1.5)	3 (1.9)	11 (1.1)

	Complete Cohort		Missing Outcome Recording for Weight		Missing Some Baseline Covariate Data	
	Sita	**Sulf**	**Sita**	**Sulf**	**Sita**	**Sulf**
Pancreatitis	32 (1.0)	197 (1.3)	17 (1.3)	114 (1.8)	0 (0)	22 (2.1)
Binary Treatment Indicator Variables¥, n(%)						
Anti-hypertensive	2209 (69.9)	10377 (69.8)	874 (66.5)	4206 (66.7)	105 (67.7)	660 (63.1)
Antiplatelets	1019 (32.2)	5933 (39.9)	373 (28.4)	2159 (34.2)	51 (32.9)	347 (33.2)
Anticoagulants	143 (4.5)	668 (4.5)	57 (4.3)	281 (4.5)	4 (2.6)	43 (4.1)
Anti-arrythmic	16 (0.5)	98 (0.7)	6 (0.5)	40 (0.6)	0 (0)	12 (1.1)
Diuretics	843 (26.7)	4082 (27.5)	298 (22.7)	1595 (25.3)	44 (28.4)	277 (26.5)
Statins	2499 (79.1)	11632 (78.3)	1009 (76.7)	4684 (74.3)	120 (77.4)	681 (65.1)
Other lipid lowering drugs	175 (5.5)	809 (5.4)	67 (5.1)	275 (4.4)	12 (7.7)	50 (4.8)
Antidepressants	566 (17.9)	2551 (17.2)	249 (18.9)	1168 (18.5)	35 (22.6)	202 (19.3)
Antipsychotics	62 (2.0)	313 (2.1)	25 (1.9)	151 (2.4)	1 (0.6)	25 (2.4)
Antiobesity	89 (2.8)	211 (1.4)	18 (1.4)	55 (0.9)	4 (2.6)	9 (0.9)
Steroids – oral/intravenous	116 (3.7)	758 (5.1)	51 (3.9)	394 (6.2)	10 (6.5)	100 (9.6)
Thyroxine	235 (7.4)	1216 (8.2)	110 (8.4)	517 (8.2)	15 (9.7)	75 (7.2)
Anti-thyroid drugs	3 (0.1)	20 (0.1)	1 (0.1)	8 (0.1)	0 (0)	1 (0.1)
Anxiolytics	141 (4.5)	733 (4.9)	59 (4.5)	436 (6.9)	12 (7.7)	92 (8.8)

*Mean Face to Face Consultation Frequency per year
**Excessive alcohol intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months prior to index date
CKD=Chronic Kidney Disease, CrCl=Creatinine Clearance estimated in ml/min, SD=Standard Deviation

9.5.3.3 Time of recording of baseline and final weight

I selected the baseline weight value recorded in the preceding 12 months that was closest to the index date. As evidenced from the histogram in Figure 9.9, the majority of baseline values for individuals clustered close to the index date. This definition of baseline weight, allowed for accepting a weight recorded within 14 days after the index date as the baseline weight. There were a few outliers where the only qualifying record for baseline weight had in fact been recorded as far back as 180-365 days before the index date.

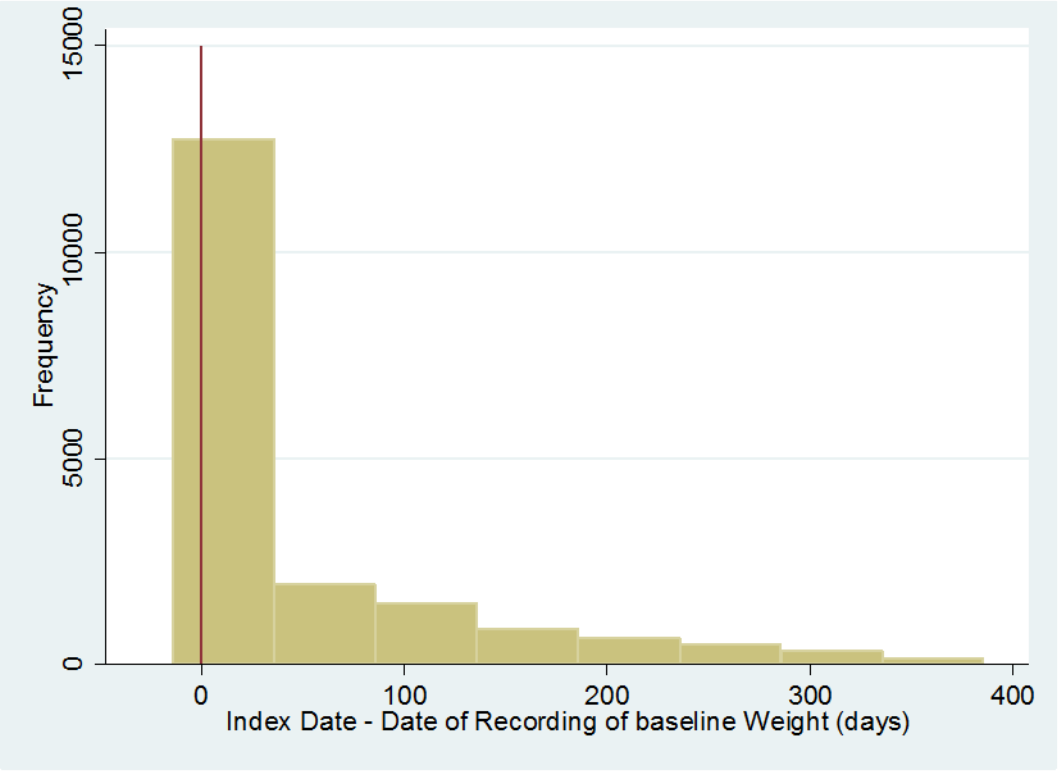


Figure 9.9 Histogram displaying distribution of time of recording of baseline weight relative to index date (date on which sitagliptin or sulphonylurea prescription was initiated)
*Note that several weight baseline recordings are recorded after the index date. This is because a weight recorded within 14 days after the index date was also accepted as a baseline weight recording (see Chapter 6, Section 6.3.1)

The final weight was recorded largely within +/-100 days of 12 months (365 days) after the index date as shown in the distribution in Figure 9.10. The final weight used in analysis was the earliest recorded at any timepoint between 9-18 months after the index date.

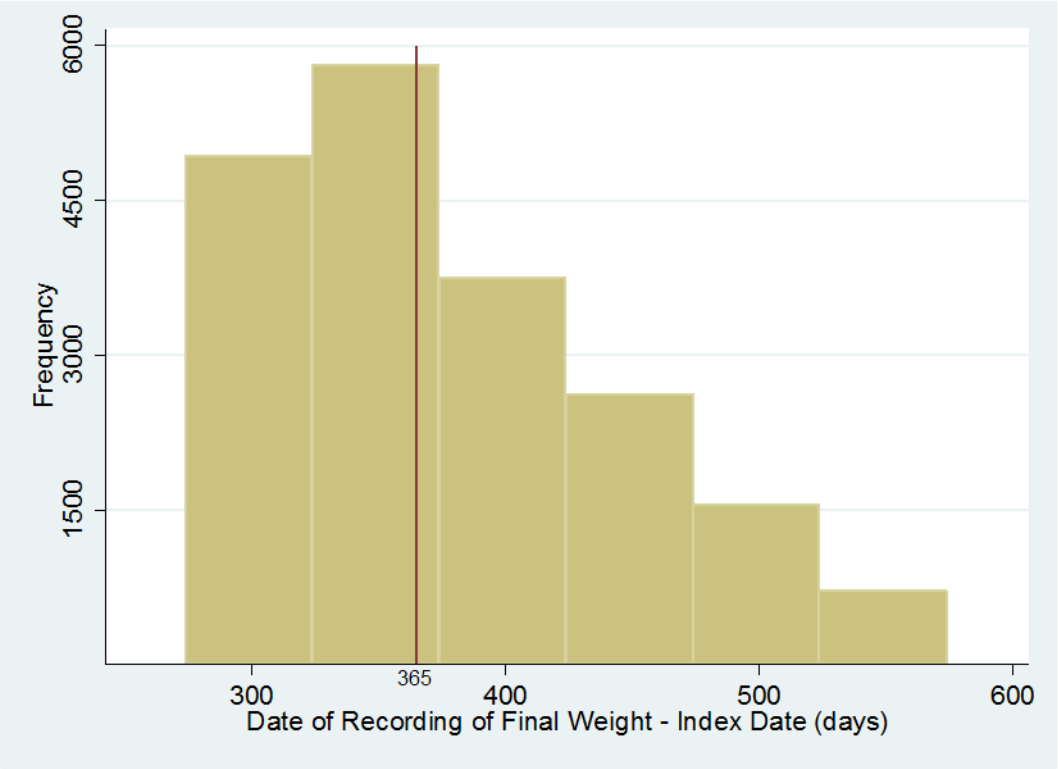


Figure 9.10 Histogram displaying distribution of time of recording of final weight relative to 365 days (1 year) after index date (date on which sitagliptin or sulphonylurea prescription was initiated)

9.5.3.4 Population level mean weight at 3 monthly intervals after the index date

The population level mean weight (for all individuals with valid weight measurements within each respective 3 monthly interval) after the index date for initiation of either sitagliptin or sulphonylureas as add-on is illustrated in Figure 9.11. A higher mean weight of around 99kg at point of initiation of sitagliptin was evident. Mean weight showed an initial increase through 3 months and some decline thereafter. In contrast, the mean weight appeared to rise steadily from around 91.5kg at baseline with sulphonylureas to around 93kg after the index date.

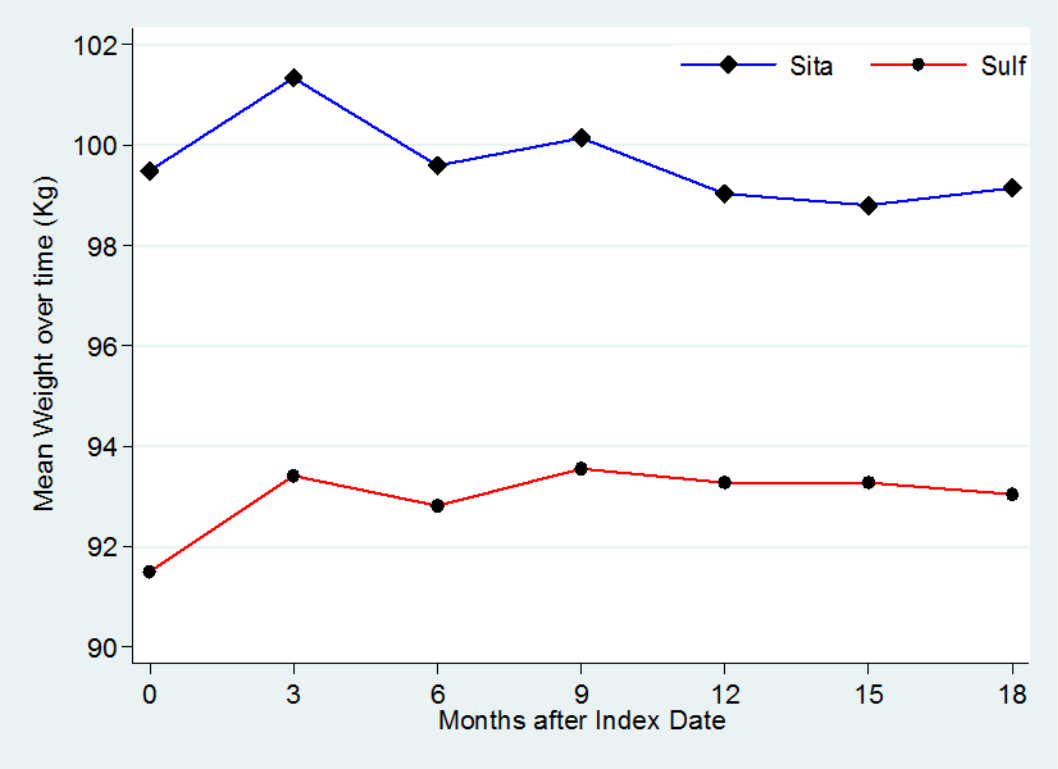


Figure 9.11 Mean weight (Kg) recorded over time (3 monthly intervals)

*Mean calculated based on all individuals with valid weight measurements for each respective 3 monthly interval

9.5.3.5 Main Analysis

There was significant effect modification by age group (aged ≥ 75 years compared to 18-75 years modified) (log likelihood ratio test for treatment by age interaction, p=0.003). Hence, the results presented for weight change were stratified by being aged 18-75 years and aged ≥ 75 years.

9.5.3.5.1 Cohort with individuals aged 18-75 years

The cohort aged 18-75 years consisted of 15,917 individuals, 2,908 prescribed sitagliptin and 13,009 prescribed sulphonylureas. At baseline, individuals prescribed sitagliptin had a mean weight of 100.8 kg, however after 12 months the mean weight reduced to 99.4 kg [paired t-test: mean reduction -1.4 kg (95% CI -1.6 to -1.2)]. For individuals prescribed sulphonylureas, the mean weight was 93.1 kg at treatment initiation and increased to 94.5 kg after 12 months [paired t-test: mean increase 1.4 kg (95% CI 1.3 to 1.5)].

After adjustment for baseline weight, sex, age and other baseline covariates identified for inclusion in the parsimonious regression model, the weight approximately 12 months after the index date was on average -2.26 kg (95% CI -2.48 to -2.04) lower for those prescribed sitagliptin compared to sulphonylureas (Table 9.6).

Therefore, though individuals prescribed sitagliptin lost weight and individuals prescribed sulphonylurea gained weight, the comparative difference in weight after 12 months was on average 2.26kg lower with sitagliptin, having accounted for baseline differences.

The results for the clinical model (after adjustment for all covariates considered theoretically to confound results) did not differ from the analysis using the parsimonious model. The Direct Acyclic Graph (Figure 9.12) details the confounders included in this analysis model. The justification for their selection is also provided in Table 9.7.

In the cohort of individuals who met the definition of "adherent" to the respective treatments, the weight approximately 12 months after the index date was on average –3.00 kg (95% CI -3.40 to -2.60) lower for those prescribed sitagliptin compared to sulphonylureas (Table 9.6).

The results for all analysis among those aged 18-75 years is included in Appendix F (Supplementary Tables 9A4-9A6) for reference.

9.5.3.5.2 Cohort with individuals aged ≥ 75 years

The cohort of individuals aged ≥ 75 years consisted of 2,106 individuals, including 252 prescribed sitagliptin and 1,854 prescribed sulphonylureas. At baseline, these older individuals prescribed sitagliptin had a mean weight of 84.7 kg. However, after approximately 12 months, the mean weight reduced to 83.1 kg [paired t-test: mean reduction -1.5 kg (95% CI -2.1 to -1.0)]. For individuals prescribed sulphonylureas, the mean weight was 80.3 kg at treatment initiation and increased slightly to 80.4 kg after approximately 12 months [paired t-test: mean increase 0.1kg, 95% CI -0.1 to 0.3)].

After adjustment for baseline weight, sex, age and other baseline covariates identified for inclusion in the parsimonious regression model, the weight approximately 12 months after the index date was on average -1.31 kg (95% CI -1.96 to -0.66) lower for those prescribed sitagliptin compared to sulphonylureas (Table 9.6). Therefore a smaller comparative reduction in weight after 12 months was evident with sitagliptin in this older group aged ≥ 75 years compared to those aged 18-75 years. These analyses results were consistent with the clinical model analyses (Table 9.6).

The analysis of the "adherent" population subgroup suggested that those older adults who remained on continuous treatment for the entire study period exhibited a greater comparative reduction in weight approximately 12 months after the index date with sitagliptin of -2.46 kg (95% CI -3.43 to -1.49).

The main results for all three regression analyses among those aged ≥ 75 years are also summarised in Table 9.6. The full output from the regression analyses for all models for those aged ≥ 75 years is also included in Appendix F (Supplementary Tables 9A7-9A9) for reference.

Table 9.6 Regression Analysis for mean difference in weight (kg) approximately 12 months after baseline for individuals aged 18-75 years and aged ≥ 75 years

Model: Sitagliptin vs Sulphonylureas	Unadjusted, mean diff (95% CI)	Adjusted for baseline weight, mean diff (95% CI)	Adjusted for Sex, Age & Baseline weight, mean diff (95% CI)	Fully Adjusted Multivariable¥, mean diff (95% CI)
Aged ≥ 18– 75 years				
Parsimonious model (n=15,917)	4.90 (4.07 to 5.72)	-2.70 (-2.92 to -2.49)	-2.61 (-2.83 to -2.4)	-2.26 (-2.48 to -2.04)
Clinical model (n=15,367)*	4.94 (4.11 to 5.78)	-2.73 (-2.95 to -2.51)	-2.64 (-2.86 to -2.43)	-2.31 (-2.54 to -2.09)
"Adherent" population (n=3,764)	1.01 (-0.61 to 2.64)	-3.34 (-3.74 to -2.95)	-3.26 (-3.65 to -2.87)	-3.00 (-3.40 to -2.60)
Aged ≥ 75 years				
Parsimonious model (n=2,106)	2.73 (0.67 to 4.78)	-1.50 (-2.14 to -0.86)	-1.49 (-2.12 to -0.86)	-1.31 (-1.96 to -0.66)
Clinical model (n=2,062)**	2.72 (0.63 to 4.80)	-1.56 (-2.21 to -0.90)	-1.55 (-2.20 to -0.91)	-1.38 (-2.04 to -0.72)
"Adherent" population (n=642)	0.67 (-2.95 to 4.30)	-2.54 (-3.49 to -1.60)	-2.54 (-3.48 to -1.61)	-2.46 (-3.43 to -1.49)

¥Mutually adjusted for baseline HbA1c, baseline weight, age, year entry, F2FC, sex, Townsend Quintile, smoking status, metformin dose, history of excessive alcohol intake, hypoglycaemia, neuropathy, heart failure, anaemias, liver disease and having a prescription within 3 months prior to the index date for diuretics, statins, antidepressants and oral/intravenous steroid medication.
*Loss of 16 individual from cohort used in parsimonious model analysis due to missing baseline smoking status and 534 individuals due to missing Townsend quintile
**Loss of 44 individuals from cohort used in parsimonious model analysis due to missing Townsend quintile
Mean diff=mean difference, CI=Confidence Interval.
Note: Individuals prescribed sulphonylureas are the reference population in all regression estimates above.

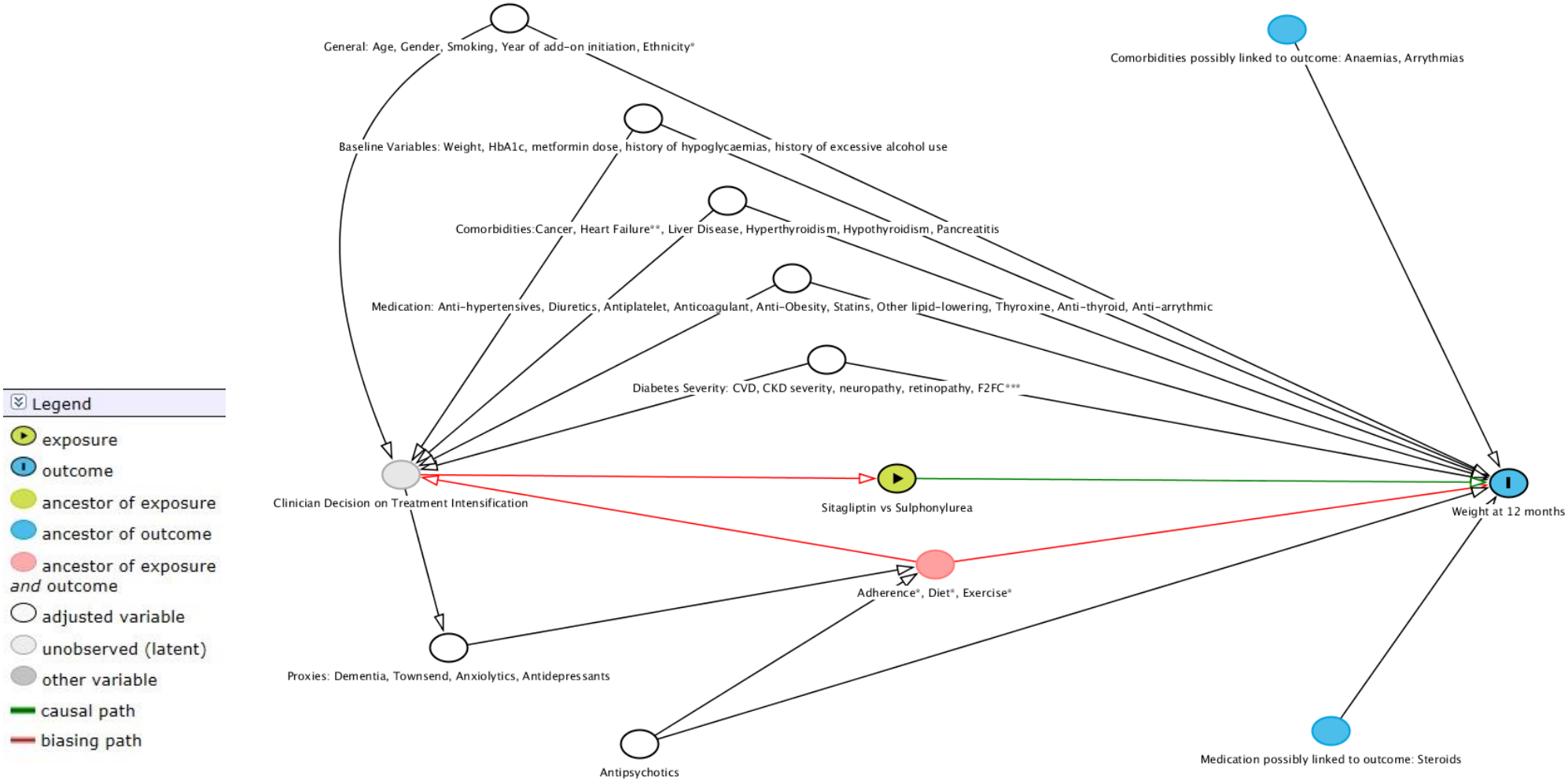


Figure 9.12 Direct Acyclic Graph depicting relationship between covariates, exposure and outcome for clinical model examining change in weight at approximately 12 months from baseline

*Ethnicity though included in DAG was not well recorded in THIN, Adherence, Diet and Exercise not recorded in THIN hence proxies used where possible

**Heart Failure refers to those with either Read code for Heart Failure recorded or on treatment

***Face to Face Consultation Frequency

CVD= Cardiovascular disease; CKD=Chronic Kidney Disease

Table 9.7 Justifications for confounder selection for clinical model for analysis on weight change

***A Priori* Confounders (measured at baseline)**	**Exposure Association**	**Outcome Association**
General		
Age at study entry	Imbalance at baseline - may affect treatment choice	Age may affect weight control
Gender	Imbalance at baseline - may affect treatment choice	Gender may affect weight control
Face to Face Consultation frequency (F2FC)	Imbalance at baseline - may affect treatment choice (for example sulphonylureas may increase weight gain therefore may want a patient with better record of attendance to allow adequate monitoring)	Intensity of management as reflected in frequency of appointments may affect likelihood of weight recording and thus control
Smoking Status	Imbalance at baseline – sulphonylureas may carry perceived higher cardiovascular risk which smoking could increase further - this may affect prescriber decision	Smoking can affect weight
Ethnicity*	Imbalance at baseline - may affect treatment choice as ethnic variation in treatment response to anti-diabetic has been reported	Ethnic variation in weight exists
Adherence**	History of poor medication adherence may affect prescriber choice of treatment	Erratic medication adherence may affect weight
Diet**	Type of diet at baseline may affect treatment choice – sulphonylureas carry higher risk of hypoglycaemias	Will affect weight
Exercise**	Level of exercise an individual undertakes may affect treatment choice at baseline	Will affect weight
Year of add-on initiation	Will effect reasons for choice of exposure – guidance on choice of exposure has changed over time	Guidance on intensity of monitoring will affect frequency of measurements which could impact weight control
Baseline Weight	Imbalance at baseline - may affect treatment choice	Weight change is outcome of interest
Baseline HbA1c	Imbalance at baseline - may affect treatment choice	HbA1c will reflect dietary glucose intake and glucose control which is strongly associated with weight
Metformin dose (<1500 or >1500)	Imbalance at baseline	Will affect dosing of sulphonylureas subsequently which will ultimately impact on weight
History of hypoglycaemias	Prescribers may favour sitagliptin where history of hypoglycaemia	Erratic glycaemic control, may lead to fluctuations in weight as well
History of excessive alcohol use	Prescriber may avoid sulphonylureas as higher risk	Can affect weight

***A Priori* Confounders (measured at baseline)**	**Exposure Association**	**Outcome Association**
	of hypoglycaemia with high alcohol intake	
Comorbidities		
Cancer	Imbalance at baseline - may affect treatment choice	Individuals with cancer may be more likely to have fluctuating weight
Cardiovascular disease (CVD)	Imbalance at baseline - may affect treatment choice	CVD can affect weight
Heart Failure (HF)	Imbalance at baseline - may affect treatment choice as conflicting signal with sitagliptin of worsening HF	HF can cause fluid overload which will affect weight
Chronic Kidney Disease	Imbalance at baseline - may affect treatment choice	Likely to affect weight
Neuropathy	Imbalance at baseline - may affect treatment choice based on perceived diabetes severity and treatment efficacy	Marker of poor diabetes control which could lead to greater weight fluctuation
Retinopathy	Imbalance at baseline - may affect treatment choice based on perceived diabetes severity and treatment efficacy	Marker of poor diabetes control which could lead to greater weight fluctuation
Liver disease	Imbalance at baseline - may affect treatment choice	Likely to affect weight
Hyperthyroidism	Imbalance at baseline - may affect treatment choice	May affect metabolism and thereby weight
Hypothyroidism	Imbalance at baseline - may affect treatment choice	May affect metabolism and thereby weight
Pancreatitis	If history of pancreatitis – prescriber may favour sulphonylurea	History of pancreatic dysfunction may increase propensity of erratic glycaemic and weight control
Medications		
Anti-hypertensive	Imbalance at baseline - may affect treatment choice e.g. Ramipril may be marker of CVD and hence affect exposure choice	Marker of poor cardiovascular health which may affect weight
Anti-arrythmics	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor cardiovascular health which may affect weight
Diuretics	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor cardiovascular health and diuretics also affect weight directly
Antiplatelet	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor cardiovascular health which may affect weight
Anticoagulant	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor cardiovascular health which may affect weight
Antiobesity	Imbalance at baseline - may affect treatment choice as clinicians may avoid	Will directly affect weight

***A Priori* Confounders (measured at baseline)**	**Exposure Association**	**Outcome Association**
	sulphonylureas due to risk of weight gain	
Statins	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Poor cardiovascular health may affect weight
Other lipid lowering drugs	Imbalance at baseline - may affect exposure choice	Poor cardiovascular health may affect weight
Thyroxine	None	Will affect thyroid function and thus weight
Anti-thyroid drugs	None	Will affect thyroid function and thus weight
Others		
Dementia	Imbalance at baseline - may affect exposure choice as sulphonylureas carry risk of hypoglycaemia	Dementia may act a weak proxy for worse adherence to medication, incapacitate individuals to exercise and affect diet - hence affect weight
Townsend Quintile	Imbalance at baseline - may affect exposure choice	Higher Townsend Quintiles (more deprived) may act a weak proxy for worse diet and adherence which would ultimately affect weight
Antidepressants	History of depression may drive prescriber to avoiding sulphonylureas as carry greater risk of hypoglycaemia	May act a weak proxy for adherence but some directly affect weight themselves
Anxiolytics	History of anxiety may drive prescriber to avoiding sulphonylureas as carry greater risk of hypoglycaemia	May act a weak proxy for adherence and thus affect weight
Variables measured at baseline which may affect outcome but not exposure	**Exposure Association**	**Outcome Association**
Comorbidities		
Arrythmias	None	Marker of poor cardiovascular health which may affect weight
Anaemias	None	Causes fatigue and lethargy which may affect diet and exercise levels which may affect weight
Medications		
Steroids – Oral/Intravenous	None	May affect weight directly
Antipsychotics	None	May act a weak proxy for adherence and several anti-psychotics directly affect weight

*Ethnicity though included in DAG was not well recorded in THIN.
**Diet, Adherence and Exercise not recorded in THIN hence proxies used where possible

9.5.3.6 Propensity Score Matching Analysis

The propensity for being prescribed sitagliptin was displayed in Figure 9.6 for the initial cohort before matching. Several variable such as weight, Townsend quintile as well as comorbidities and prescribed medication were significantly different before matching in the sitagliptin and

sulphonylurea groups as shown in Table 9.8. However, propensity score matching was highly successful and no variable including weight (which was significantly different pre-matching) showed significant difference after matching.

Table 9.8 Standardised Differences and Chi-squared tests before and after propensity-score matching for analysis on weight change

	Pre-matching				**Post-matching**			
	Sita	**Sulf**	**Stand Diff**	**P-value**	**Sita**	**Sulf**	**Stand Diff**	**P-value**
Total	**3160**	**14863**			**3160**	**3160**		
Baseline Weight kg, mean (SD)	99.5 (21.8)	91.5 (19.6)	0.386	**<0.001**	99.5 (21.8)	99.3 (22.4)	0.004	0.671
Age at index date years, mean (SD)	58.8 (11.2)	61.2 (11.7)	-0.212	**<0.001**	58.8 (11.2)	58.7 (11.7)	0.006	0.804
Sex, n(%)								
Male	1871 (59.2)	9113 (61.3)	-0.043	0.028	1871 (59.2)	1873 (59.3)	-0.001	0.959
Female	1289 (40.8)	5750 (38.7)			1289 (40.8)	1287 (40.7)		
Baseline HbA1c mmol/mol, mean (SD)	70.4 (14.7)	74.4 (18.9)	-0.234	**<0.001**	70.4 (14.7)	70.7 (15.4)	0.010	0.371
Year Entry, n(%)				**<0.001***				0.979*
2007	25 (0.8)	1775 (11.9)			25 (0.8)	25 (0.8)		
2008	110 (3.5)	2369 (15.9)			110 (3.5)	103 (3.3)		
2009	359 (11.4)	2697 (18.1)			359 (11.4)	341 (10.8)		
2010	757 (24.0)	2467 (16.6)			757 (24.0)	758 (24.0)		
2011	648 (20.5)	2145 (14.4)			648 (20.5)	661 (20.9)		
2012	697 (22.1)	1804 (12.1)			697 (22.1)	686 (21.7)		
2013	511 (16.2)	1466 (9.9)			511 (16.2)	536 (17.0)		
2014	53 (1.7)	140 (0.9)			53 (1.7)	50 (1.6)		
F2FC**, mean (SD)	7.3 (5.1)	7.5 (5.0)	-0.027	0.160	7.3 (5.1)	7.3 (5.2)	-0.002	0.923
CKD Stage, n(%)				**<0.001***				0.987*
(CrCl>60 ml/min)	2817 (89.1)	12248 (82.4)			2817 (89.1)	2813 (89.0)		
(CrCl 30-59 ml/min)	343 (10.9)	2615 (17.6)			343 (10.9)	347 (11.0)		
(CrCl<30 ml/min)	0 (0)	0 (0)			0 (0)	0 (0)		
Binary Comorbidity Indicator Variables¥, n(%)	0 (0)	0 (0)						
Heart failure	328 (10.4)	1673 (11.3)	0.028	0.154	328 (10.4)	330 (10.4)	0.002	0.934
Binary Treatment Indicator Variables, n(%)								
Anticoagulants	143 (4.5)	668 (4.5)	-0.001	0.939	143 (4.5)	151 (4.8)	0.012	0.633
Antipsychotics	62 (2.0)	313 (2.1)	0.010	0.607	62 (2.0)	72 (2.3)	0.022	0.383
Steroids –oral/iv	116 (3.7)	758 (5.1)	0.070	**0.001**	116 (3.7)	124 (3.9)	0.013	0.599

*P-value derived from chi squared test. **Mean Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months prior to index date
CKD stage=chronic kidney stage, CrCl=Creatinine Clearance estimated in ml/min, SD=Standard Deviation
Note: For purposes of weight change matching, CKD stage was made binary (as opposed to three categories) due to problems of perfect prediction in matching when 3 categories were used.
Note 2: P-values in bold are statistically significant at <0.05 level.

Further evidence of successful matching is also provided in Figure 9.13 where nearly complete overlap of both sitagliptin and sulphonylurea curves suggests a similar distribution of measured covariates across both groups at baseline.

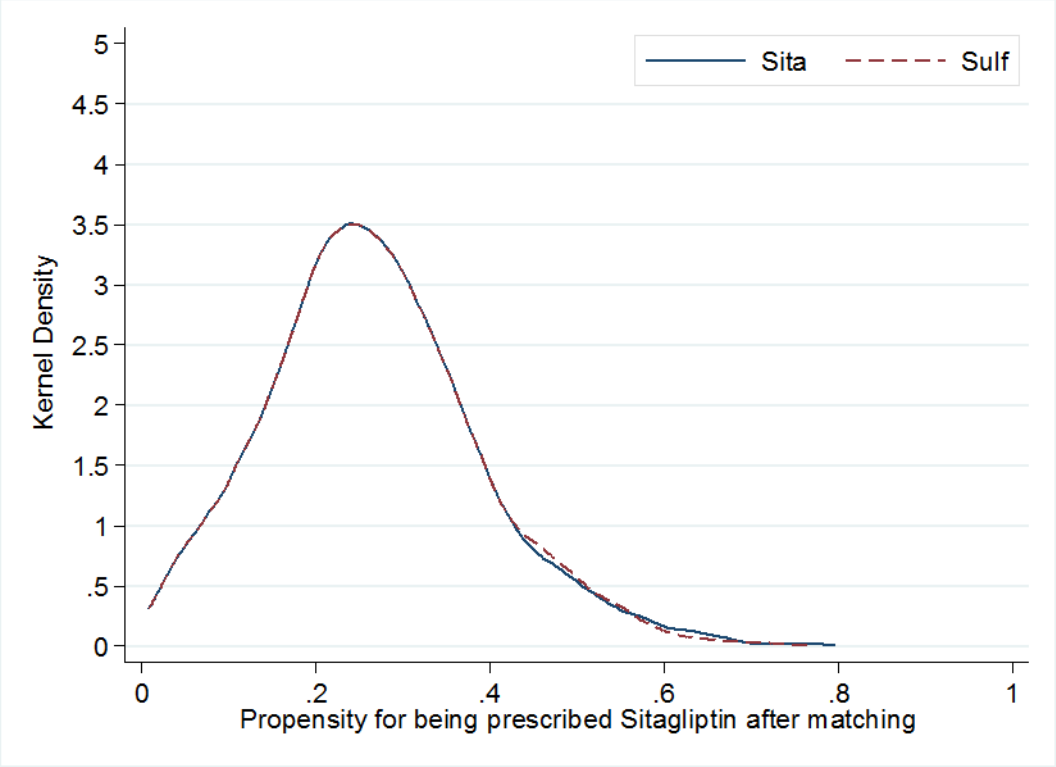


Figure 9.13 Kernel density plot of propensity for being prescribed sitagliptin based on distribution of measured characteristics at baseline for both individuals prescribed sitagliptin and sulphonylureas after matching (analysis on weight change)

The Average Treatment Effect estimated for the analysis on weight change for 3,160 matched pairs was -2.30 kg (95% CI -3.05 to -1.56). This finding was similar to that observed with the main regression analysis. This suggested the weight approximately 12 months after the index date was on average 2.3kg lower for those prescribed sitagliptin compared to sulphonylureas, after matching.

When matching was stratified by age, analysis of 5,816 individuals aged 18-75 years (2,908 matched pairs) prescribed sitagliptin or sulphonylureas respectively yielded an Average Treatment Effect estimate of -2.55 kg (95% CI -3.26 to -1.84). While, for the individuals aged ≥ 75 years (252 matched pairs), analysis yielded an Average Treatment Effect estimate of -2.40 kg (95% CI -4.72 to -0.41). Although a similar estimate was obtained with propensity score matching analysis for those aged 18-75 years, the analysis in the older adults aged ≥ 75 years suggested a numerically greater treatment difference than that obtained with regression (-2.4kg vs -1.3kg).

However, propensity score matching analysis was undertaken on a much smaller cohort of (504 compared to 2,106) and the confidence intervals for estimates from both regression and propensity score matching analyses did overlap.

9.6 Discussion

9.6.1 Key Findings

In this chapter, I found that the reduction in HbA1c measured approximately 12 months after baseline was 0.89 mmol/mol (95% CI 0.33 to 1.45) less when sitagliptin was added to metformin instead of sulphonylureas for individuals aged ≥ 18 years, while no difference was observed among older individuals aged ≥ 75 years. Though this overall result was statistically significant, it was clinically of little consequence as it represents a negligible difference in glycaemic control. The supportive analysis undertaken using the clinical model, propensity score matching method and including the cohort of "adherent" individuals all supported this conclusion. In contrast, a clinically significant, comparative reduction in weight was observed at 12 months with sitagliptin compared to sulphonylureas of -2.26 kg (95% CI -2.48 to -2.04) in individuals aged 18-75 years while a smaller -1.31kg (95% CI -1.96 to -0.66) weight difference was observed among older individuals aged ≥ 75 years. This weight difference was driven by weight reduction observed in the sitagliptin group of around 1.4kg and weight gain with sulphonylureas of around 1.4kg. The weight gain with sulphonylureas was however, only observed among individuals aged 18-75 years and not in the ≥ 75 age group. All supportive analysis undertaken including propensity score matching analyses were consistent with these findings for change in weight.

9.6.2 Handling Missing Data

The main reason for loss of individuals for analysis from our initial cohort was due to the absence of outcome data (a final recording value for HbA1c or weight between 9-18 months after the index date). Baseline data in general was very well recorded with 8.1% missing baseline data for the analysis on HbA1c change and 4.5% missing baseline data for the analysis on weight change. To investigate impact of missing data, I undertook an in depth analysis comparing the complete cohort used for analysis to the cohort missing outcome data and cohort missing some baseline data (Section 9.5.2.2 for HbA1c and Section 9.5.3.2 for weight). This is recommended good practice when investigating the impact of missing data on analyses.[172,173] The results of these analyses showed that the characteristics of the individuals prescribed sitagliptin and sulphonylureas across these three groups: cohort with complete data, cohort with missing

outcome data and cohort missing some baseline data were highly similar and exhibited little variation.

9.7 Context of this chapter in overall work

In this chapter, I have presented the results from cohort studies examining change in HbA1c and weight with sitagliptin compared to sulphonylureas as add-on to metformin. In Chapter 11, I will highlight the strengths and limitations of this study, place my findings in the context of existing literature and also describe the implications of this work for clinical practice, public health and future research. Prior to this discussion, I will first present cohort studies comparing sitagliptin and sulphonylureas add-on to metformin for time before first recording of a HbA1c > 58 mmol/mol and time before first anti-diabetic treatment regimen change was introduced in Chapter 10.

Chapter 10 Cohort studies examining first recording of a HbA1c > 58 mmol/mol and first recording of a treatment regimen change

10.1 Chapter Overview

In this chapter, I will examine the remaining two outcomes of interest in evaluating the effectiveness of sitagliptin compared to sulphonylureas in individuals with T2DM (type 2 diabetes mellitus) inadequately controlled on metformin. I will investigate the time to: 1) first recording of a HbA1c > 58 mmol/mol and 2) first change in the anti-diabetic treatment regimen. I will examine these outcomes initially among all individuals aged ≥ 18 years and then investigate if there is any difference in effectiveness for these outcomes between those aged 18-75 years and older adults aged ≥75 years.

10.2 Rationale for study

In Chapter 9, I was able to provide "real world" evidence demonstrating a similar HbA1c reduction with sitagliptin and sulphonylureas approximately 12 months after baseline when added to metformin. I also observed a clinically significant reduction in weight at 12 months with sitagliptin when compared to sulphonylureas. I demonstrated that this glycaemic benefit and comparative weight reduction was also evident in a more comorbid "real world" cohort as well as in older individuals aged ≥75 years, a subgroup of individuals excluded from many studies previously undertaken.

However, a reduction in HbA1c and weight does not necessarily alone, translate to an effectiveness of treatments if "real world" patients are not actually meeting glycaemic targets for optimum diabetes control, or having their treatment changed soon after initiation. A change in the treatment regimen could indicate both an intolerance to the sitagliptin or sulphonylureas for the individual or insufficient effectiveness of the treatments. The analysis in this chapter will focus on identifying and analysing the time to these two important events.

1. The first date on which a HbA1c of > 58 mmol/mol (7.5%) is recorded. This threshold of 58 mmol/mol is the cut-off above which treatment change (intensification or switching if necessary e.g. due to intolerance) is recommended by NICE (see Chapter 7, Section 7.2 for further detail).[22]

2. The first date on which an anti-diabetic treatment regimen change is introduced (i.e. prescribing of an anti-diabetic other than metformin or the add-on treatment, sitagliptin or sulphonylureas).

I will also bring both cohort study analyses together in the final section where I will assess the clinician response for those individuals who had a recording of a HbA1c > 58 mmol/mol. I will determine if they had their treatment changed, dosage changed (where dosage information is available) or had no change made.

10.3 Study Objectives

1. To examine the time to first recording of a HbA1c > 58 mmol/mol among individuals aged ≥ 18 prescribed sitagliptin or sulphonylureas as add-on to metformin.
2. To investigate whether the rate of recording of a HbA1c > 58 mmol/mol in 1) differs in individuals aged ≥ 75 years compared to those aged 18-75 years
3. To examine the time to first anti-diabetic treatment regimen change among individuals aged ≥ 18 prescribed sitagliptin or sulphonylureas as add-on to metformin.
4. To investigate whether the rate of recording of an anti-diabetic treatment regimen change in 3) differs in individuals aged ≥ 75 years compared to those aged 18-75 years
5. To descriptively assess clinician response to recording of a HbA1c > 58 mmol/mol for an individual by determining if a treatment change was introduced, doses were changed or no action was taken.

10.4 Methods

10.4.1 Study Population

The cohort of individuals included in the analyses to follow and a summary of their demographic and clinical characteristics have been described in detail in Chapter 6 (Section 6.4.1). The full analysis cohort is comprised of individuals with T2DM who were issued at least one prescription for either sitagliptin or sulphonylureas as add-on to metformin between 2007 and 2014. Scientific approval to undertake this study was obtained from CMD Medical Research's Scientific Review Committee in August 2016. (SRC Reference Number: 16-072).

10.4.2 Statistical Analysis

I examined both time to first recording of a HbA1c > 58 mmol/mol and time to first date on which an anti-diabetic treatment regimen change was recorded using a multivariable cox regression analyses in 2 separate cohort studies. All individuals included in the analysis were required to

have at least one recording for a HbA1c between 3 months and 30 months after the index date for initiation of add-on treatment with sitagliptin or sulphonylureas. I did not include any HbA1c recording within the first 3 months after the index date for analysis, in order to allow a reasonable period of time for the add-on treatments to have an actual glycaemic effect. Individuals were followed up from the index date till they left the practice, died, had a recording of one of the outcomes detailed above or for a maximum of 30 months (2.5 years).

I have shown in Chapter 7 (Section 7.4.2.1) that the frequency of recording of HbA1c is similar across both sitagliptin and sulphonylurea cohorts. This supports the underlying assumption for the analysis on time to first HbA1c > 58 mmol/mol recording that both individuals prescribed sitagliptin and sulphonylureas have equal possibility to have a HbA1c recorded at any timepoint after the index date (be that > 58 mmol/mol or ≤ 58 mmol/mol).

Kaplan-Meier graphs were used initially to illustrate the difference between the two treatments for both outcomes. I then presented three Cox regression models in turn for both outcomes. These included an unadjusted analyses, analyses adjusted for sex and age and also a multivariable Cox regression analyses adjusting for covariates that I have shown to have significant association with treatment selection (sitagliptin or sulphonylureas) and each outcome (as detailed in Chapters 6 and 7). I examined validity for the proportional hazards assumption which underlies a Cox regression analysis through examination of scaled Schoenfeld residual plots against time for the cohort studies examining each outcome and found no evidence of departure from this assumption.[141]

I tested these models for evidence of effect modification by age, via interactions between treatment and age group (among those older individuals aged ≥ 75 vs those aged 18-75 years).[141] There was no evidence of effect modification by age group in the analysis examining time to first recording of a HbA1c > 58 mmol/mol. However this interaction was evident for the analysis on time to first recording of an antidiabetic treatment regimen change. Thus, I presented these latter results stratified by those aged 18-75 years and those aged ≥ 75 years.

I investigated whether there was evidence of clustering by practice in both analysis through the use of random effects models with a random intercept term included for each practice.[141] These models showed no evidence of significant practice effects for either outcome.

In addition to these models, I have presented further supporting analyses as detailed below:

1. Multivariable analyses adjusting for all covariates deemed to have a theoretical association with exposure and outcome. This was referred to as the clinical model and the corresponding Direct Acyclic Graphs (DAGs) were also presented.
2. Subgroup analyses including only those individuals who were intensified with another third anti-diabetic treatment as add-on to metformin and sitagliptin or sulphonylureas respectively.
3. Subgroup analysis including only those individuals who were switched from either sitagliptin or sulphonylureas to another anti-diabetic treatment.
4. Subgroup analyses including only those individuals who were issued prescriptions for metformin and either of sitagliptin or sulphonylureas (including combination pills) for at least 30 months (with no more than 60 days gap between successive prescriptions). This group was referred to as the "adherent" cohort with the caveat that this definition using issue of continuous prescriptions was only a surrogate measure for true adherence. That is, continuous prescribing is necessary, but not alone sufficient, for actual adherence to treatment.

The final analysis was descriptive and helped assess clinician response to recording of a HbA1c > 58 mmol/mol among those initiated on sitagliptin or sulphonylureas by determining if a treatment change was introduced, doses were changed or no action was taken. Treatment change was classified as a switch (if sitagliptin or sulphonylurea were stopped in place of another anti-diabetic treatment) or intensification (if a third-line anti-diabetic treatment was added to the regimen). To count as intensification all three anti-diabetic treatments (metformin, sitagliptin or sulphonylurea and new third-line treatment) must have been issued within the 60 days after initiation of third-line treatment. Dosing information is not always recorded in THIN. In instances where the dose had not been recorded on the prescription, it was calculated manually based on quantity issued and duration of the prescription where this was available. In some instances, it was not possible to calculate doses prescribed.

10.5 Results

10.5.1 Cohort Size

Details of cohort sizes for the initial cohorts and then for the cohorts with complete data (with no missing baseline or outcome data) to facilitate analysis on time to first HbA1c > 58 mmol/mol and first treatment change is provided in Table 10.1. In total, there were 26,844 individuals, 4,630

(17%) prescribed sitagliptin and 22,214 (83%) prescribed sulphonylureas. After excluding individuals with no recorded HbA1c between 3 months and 30 months (2.5 years) after the index date and those who were missing some baseline data there were 23,601 individuals left (4,124 (17%) prescribed sitagliptin and 19,477 (83%) prescribed sulphonylureas). Further details of the subgroups is also provided in Table 10.1.

Table 10.1 Cohort Sizes for analysis on time to first HbA1c > 58 mmol/mol and first anti-diabetic treatment regimen change

Cohort		Total	Sitagliptin	Sulphonylureas
Full Population	Number of Individuals	**26,844**	4,630 (17%)	22,214 (83%)
	Aged ≥ 75 years	**3,324**	407 (12%)	2,917 (88%)
	Intensified	**4,004**	936 (23%)	3,068 (77%)
	Switched	**3,593**	944 (26%)	2,649 (74%)
	"Adherent" to Medications for 30 months*	**7,379**	1,108 (15%)	6,271 (85%)
Complete Cohort for analysis on HbA1c > 58 mmol/mol and analysis on treatment regimen change**	Number of Individuals	**23,601**	4,124 (17%)	19,477 (83%)
	Aged≥ 75 years	**2,847**	344 (12%)	2,503 (88%)
	Intensified	**3,654**	869 (24%)	2,785 (76%)
	Switched	**3,232**	870 (27%)	2,362 (73%)
	"Adherent" to Medications for 30 months*	**6,846**	1,040 (15%)	5,806 (85%)

*"Adherent" to both metformin and sitagliptin or sulphonylureas as defined by no greater than 60 day gap between successive prescriptions for 18 months.
**This is the number of individuals with at least one recording for HbA1c between 3-30 months after the index date and recorded baseline data for other covariates needed for analyses models.

10.5.2 Flow diagram illustrating complete cohort size for analysis

A detailed breakdown of how I arrived at the final complete cohort size of 23,601 individuals for the analysis on time to first recording of a HbA1c > 58 mmol/mol and time to first recording of a treatment regimen change is presented in Figure 10.1.

The cause for loss of individuals was mostly due to missing baseline data, largely for HbA1c and weight (Figure 10.1).

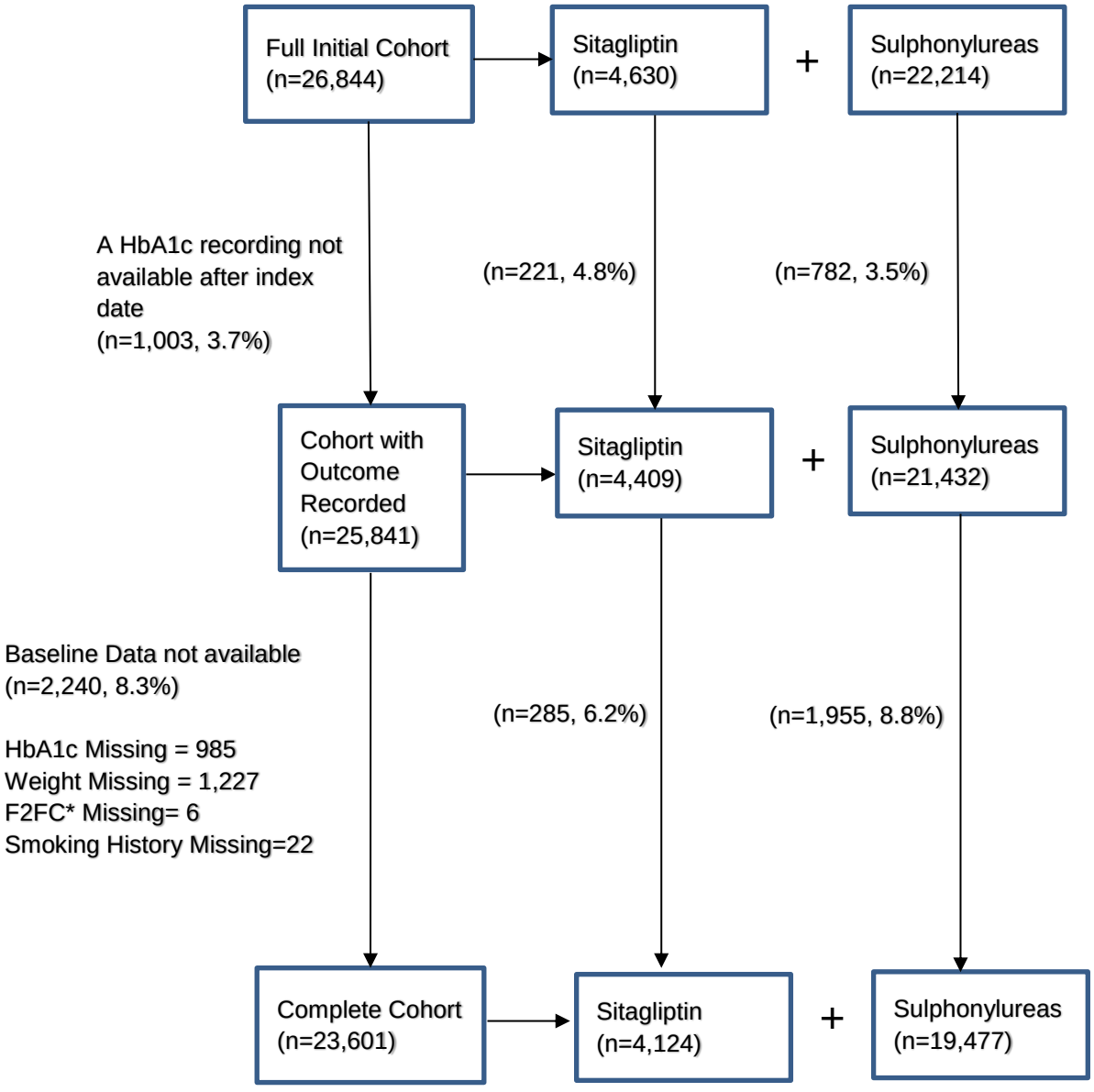


Figure 10.1 Flow diagram illustrating attrition from full initial cohort to final complete cohort used for analysis
*F2FC= Mean Face to Face Consultation Rate per year
Note: All percentage reductions in cohort size are calculated based on loss from full initial cohort

10.5.3 Baseline characteristics of complete cohort compared to cohort with missing recording for HbA1c after the index date and cohort missing baseline data

The baseline characteristics of all individuals initiated on sitagliptin vs sulphonylureas after metformin are detailed in Table 10.2 for the complete cohort (with no missing data) as well as the

cohort missing recording for a HbA1c between 3-30 months after the index date and the cohort missing data for at least 1 baseline covariate (i.e. missing at least 1 of: HbA1c, weight, smoking or face to face consultation frequency – see Figure 10.1).

This table highlights that the complete cohort and cohorts missing data were highly similar for the majority of covariates. One difference to highlight includes a marginally higher baseline mean HbA1c among sitagliptin and sulphonylurea cohorts that were missing HbA1c recording after index date and cohort missing some baseline data (70.9 mmol/mol vs 76.7 mmol/mol vs 78.3 mmol/mol for sitagliptin). While for sulphonylureas, mean HbA1c at baseline was; (75.0 mmol/mol vs 78.3 mmol/mol vs 82.7 mmol/mol). The standard deviations for HbA1c across all groups were in excess of 15 mmol/mol indicating wide variability.

The percentage with a history of retinopathy: (16.6% vs 14.9 vs 9.8% for sitagliptin and 13.9% vs 13.0% vs 8.5% for sulphonylureas), and prescribed statins at baseline: (79.0% vs 72.9% vs 73.0% for sitagliptin and 77.8 % vs 73.5% vs 65.3% for sulphonylureas) was also notably different in the complete cohort compared to cohorts that were missing recording for HbA1c after the index date and cohort missing some baseline data respectively. However given the significant disparity in the size of the complete cohort and cohorts missing data, no major differences were found in measured covariates which would be considered likely to bias the analysis.

Table 10.2 Baseline characteristics of complete cohort, cohort missing outcome data and cohort missing baseline data for analysis

	Complete Cohort		**Missing Recording for HbA1c after index date**		**Missing Some Baseline Covariate Data**	
	Sita	**Sulf**	**Sita**	**Sulf**	**Sita**	**Sulf**
Total (n)	**4124**	**19477**	**221**	**782**	**285**	**1955**
Baseline HbA1c mmol/mol, mean (SD)	70.9 (15.1)	75.0 (19.2)	76.7 (18.2)	78.3 (20.3)	78.3 (20.3)	82.7 (23.2)
Missing, n(%)	0 (0)	0 (0)	0 (0)	0 (0)	124 (43.5)	861 (44.0)
Age at index date years, mean (SD)	58.9 (11.3)	61.1 (11.9)	56.1 (13.3)	59.4 (12.8)	59.8 (13.2)	60.8 (13.7)
Sex, n(%)						
Male	2479 (60.1)	11962 (61.4)	144 (65.2)	506 (64.7)	146 (51.2)	1164 (59.5)
Female	1645 (39.9)	7515 (38.6)	77 (34.8)	276 (35.3)	139 (48.8)	791 (40.5)
Baseline weight kg, mean (SD)	99.5 (22.0)	91.4 (19.8)	100.6 (23.4)	91.7 (20.4)	96.9 (23.4)	92.1 (21.8)
Missing, n(%)	0 (0)	0 (0)	0 (0)	0 (0)	182 (63.9)	1271 (65.0)
Year Entry, n(%)						
2007	29 (0.7)	2119 (10.9)	1 (0.5)	31 (4.0)	3 (1.1)	224 (11.5)
2008	125 (3.0)	2885 (14.8)	0 (0.0)	44 (5.6)	15 (5.3)	285 (14.6)
2009	437 (10.6)	3346 (17.2)	7 (3.2)	75 (9.6)	23 (8.1)	290 (14.8)
2010	901 (21.8)	3050 (15.7)	9 (4.1)	56 (7.2)	65 (22.8)	281 (14.4)
2011	779 (18.9)	2666 (13.7)	23 (10.4)	59 (7.5)	53 (18.6)	254 (13.0)
2012	873 (21.2)	2404 (12.3)	15 (6.8)	86 (11.0)	49 (17.2)	245 (12.5)
2013	706 (17.1)	2161 (11.1)	44 (19.9)	155 (19.8)	51 (17.9)	234 (12.0)
2014	274 (6.6)	846 (4.3)	122 (55.2)	276 (35.3)	26 (9.1)	142 (7.3)

	Complete Cohort		Missing Recording for HbA1c after index date		Missing Some Baseline Covariate Data	
	Sita	**Sulf**	**Sita**	**Sulf**	**Sita**	**Sulf**
F2FC*, mean (SD)	7.3 (5.1)	7.4 (5.1)	7.7 (7.9)	6.7 (4.7)	7.3 (6.1)	7.3 (5.2)
Townsend Quintile, n(%)						
1 (least deprived)	953 (23.1)	3938 (20.2)	40 (18.1)	161 (20.6)	65 (22.8)	377 (19.3)
2	821 (19.9)	3995 (20.5)	32 (14.5)	128 (16.4)	48 (16.8)	365 (18.7)
3	953 (23.1)	3938 (20.2)	40 (18.1)	161 (20.6)	65 (22.8)	377 (19.3)
4	779 (18.9)	3900 (20.0)	57 (25.8)	156 (19.9)	66 (23.2)	407 (20.8)
5 (most deprived)	589 (14.3)	2959 (15.2)	39 (17.6)	144 (18.4)	44 (15.4)	284 (14.5)
Missing, n(%)	143 (3.5)	619 (3.2)	9 (4.1)	33 (4.2)	7 (2.5)	67 (3.4)
Smoking Status, n(%)						
Non	1949 (47.3)	8932 (45.9)	94 (42.5)	368 (47.1)	130 (45.6)	876 (44.8)
Ex	1266 (30.7)	5905 (30.3)	67 (30.3)	198 (25.3)	78 (27.4)	514 (26.3)
Current	909 (22.0)	4640 (23.8)	60 (27.1)	216 (27.6)	74 (26.0)	533 (27.3)
CKD Stage, n(%)						
(CrCl>60 ml/min)	3670 (89.0)	16063 (82.5)	199 (90.0)	663 (84.8)	244 (85.6)	1674 (85.6)
(CrCl 30-59 ml/min)	451 (10.9)	3361 (17.3)	22 (10.0)	114 (14.6)	41 (14.4)	279 (14.3)
(CrCl<30 ml/min)	3 (0.1)	53 (0.3)	0 (0)	5 (0.6)	0 (0)	2 (0.1)
Metformin Dose at Baseline						
<1500mg	3229 (78.3)	14998 (77.0)	172 (77.8)	577 (73.8)	190 (66.7)	1280 (65.5)
≥1500mg	895 (21.7)	4479 (23.0)	49 (22.2)	205 (26.2)	95 (33.3)	675 (34.5)
Sulphonylurea Type, n(%)						
Gliclazide	-	17886 (91.8)	-	731 (93.5)	-	1852 (94.7)
Glipizide	-	582 (3.0)	-	15 (1.9)	-	32 (1.6)
Glibenclamide	-	112 (0.6)	-	3 (0.4)	-	15 (0.8)
Tolbutamide	-	97 (0.5)	-	1 (0.1)	-	5 (0.3)
Glimepiride	-	1466 (7.5)	-	38 (4.9)	-	108 (5.5)
Chlorpropamide	-	0 (0)	-	0 (0)	-	0 (0)
Other	-	0 (0)	-	0 (0)	-	1 (0.1)
Binary Comorbidity Indicator Variables, n(%)						
Excessive alcohol intake**	630 (15.3)	2785 (14.3)	28 (12.7)	118 (15.1)	28 (9.8)	251 (12.8)
History of Hypoglycaemia	23 (0.6)	164 (0.8)	2 (0.9)	8 (1.0)	0 (0)	9 (0.5)
Neuropathy	139 (3.4)	782 (4.0)	7 (3.2)	34 (4.3)	11 (3.9)	78 (4.0)
Retinopathy	686 (16.6)	2711 (13.9)	33 (14.9)	102 (13.0)	28 (9.8)	167 (8.5)
Cardiovascular disease	1051 (25.5)	5716 (29.3)	58 (26.2)	204 (26.1)	72 (25.3)	613 (31.4)
Heart failure	417 (10.1)	2199 (11.3)	30 (13.6)	77 (9.8)	39 (13.7)	325 (16.6)
Anaemias	356 (8.6)	1661 (8.5)	19 (8.6)	75 (9.6)	30 (10.5)	191 (9.8)
Dementia	24 (0.6)	115 (0.6)	4 (1.8)	9 (1.2)	4 (1.4)	40 (2.0)
Liver disease	146 (3.5)	726 (3.7)	11 (5.0)	40 (5.1)	11 (3.9)	44 (2.3)
Arrythmias	273 (6.6)	1491 (7.7)	17 (7.7)	56 (7.2)	22 (7.7)	156 (8.0)
Cancer	540 (13.1)	2789 (14.3)	32 (14.5)	126 (16.1)	42 (14.7)	267 (13.7)
Hypothyroidism	329 (8.0)	1627 (8.4)	16 (7.2)	55 (7.0)	28 (9.8)	140 (7.2)
Hyperthyroid	46 (1.1)	277 (1.4)	2 (0.9)	11 (1.4)	5 (1.8)	27 (1.4)
Pancreatitis	45 (1.1)	276 (1.4)	3 (1.4)	12 (1.5)	1 (0.4)	45 (2.3)
Binary Treatment Indicator Variables¥, n(%)						
Anti-hypertensive	2873 (69.7)	13493 (69.3)	130 (58.8)	512 (65.5)	185 (64.9)	1238 (63.3)
Antiplatelets	1294 (31.4)	7556 (38.8)	63 (28.5)	221 (28.3)	86 (30.2)	662 (33.9)
Anticoagulants	181 (4.4)	869 (4.5)	14 (6.3)	37 (4.7)	9 (3.2)	86 (4.4)
Anti-arrythmic	20 (0.5)	129 (0.7)	1 (0.5)	3 (0.4)	1 (0.4)	18 (0.9)

	Complete Cohort		Missing Recording for HbA1c after index date		Missing Some Baseline Covariate Data	
	Sita	Sulf	Sita	Sulf	Sita	Sulf
Diuretics	1058 (25.7)	5237 (26.9)	47 (21.3)	164 (21.0)	80 (28.1)	553 (28.3)
Statins	3259 (79.0)	15146 (77.8)	161 (72.9)	575 (73.5)	208 (73.0)	1276 (65.3)
Other lipid lowering drugs	222 (5.4)	1014 (5.2)	8 (3.6)	33 (4.2)	24 (8.4)	87 (4.5)
Antidepressants	744 (18.0)	3378 (17.3)	45 (20.4)	154 (19.7)	61 (21.4)	389 (19.9)
Antipsychotics	80 (1.9)	417 (2.1)	6 (2.7)	21 (2.7)	2 (0.7)	51 (2.6)
Antiobesity	103 (2.5)	255 (1.3)	3 (1.4)	7 (0.9)	5 (1.8)	13 (0.7)
Steroids –oral/iv	147 (3.6)	1037 (5.3)	11 (5.0)	40 (5.1)	19 (6.7)	175 (9.0)
Thyroxine	315 (7.6)	1609 (8.3)	17 (7.7)	51 (6.5)	28 (9.8)	148 (7.6)
Anti-thyroid drugs	4 (0.1)	23 (0.1)	0 (0)	2 (0.3)	0 (0)	4 (0.2)
Anxiolytics	183 (4.4)	1031 (5.3)	11 (5.0)	47 (6.0)	18 (6.3)	183 (9.4)

*Mean Face to Face Consultation Frequency per year
**Excessive alcohol intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months prior to index date
CKD=Chronic Kidney Disease, CrCl=Creatinine Clearance estimated in ml/min, SD=Standard Deviation

10.5.4 Time to first recording of a HbA1c > 58 mmol/mol

10.5.4.1 Graphical evaluation of time to first recording of HbA1c > 58 mmol/mol

The Kaplan Meier graph displaying the time to first recording of a HbA1c > 58 mmol/mol over follow-up (starting 3 months after the index date) is illustrated in Figure 10.2. It illustrates that both sitagliptin and sulphonylurea initiators follow very similar trajectories for their first recordings of a HbA1c > 58 mmol/mol.

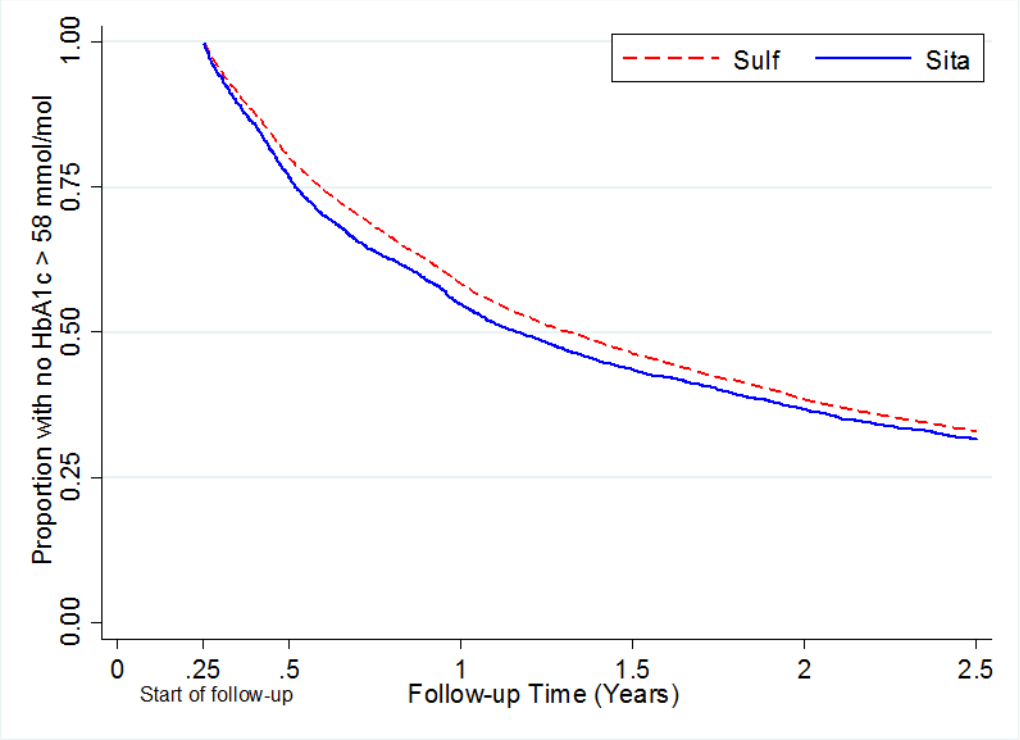


Figure 10.2 Kaplan Meier curve for recording of a HbA1c > 58 mmol/mol
*Note start of follow-up for this analysis was purposefully at 3 months (0.25 years) in order to allow add-on of sitagliptin or sulphonylureas respectively to have a glycaemic effect i.e. HbA1c recordings within 3 months of the index date were not considered for analysis

10.5.4.2 Main analysis

In total, 2,695 (65.3%) of all individuals treated with sitagliptin and 12,476 (64.0%) of all individuals treated with sulphonylureas had a record of HbA1c > 58 mmol/mol during the study follow-up.

Individuals aged ≥ 18 years prescribed sitagliptin as add-on compared to sulphonylureas had a slightly elevated risk of recording a HbA1c > 58 mmol/mol before adjustment, [Hazard Ratio 1.09 (95% CI 1.05 to 1.14)] (Table 10.3). After adjustment for baseline HbA1c, sex, age and other covariates identified for inclusion in the parsimonious regression model, there still remained a 11% increased risk [HR 1.11 (95% CI 1.06 to 1.16)].

The results for the clinical model (after adjustment for all covariates considered theoretically to confound results) did not differ from the analysis using the parsimonious model. The Direct Acyclic Graph (Figure 10.3) details the confounders included in this analysis model. The justification for their selection is provided in detail in Table 10.4.

In the first subgroup analysis, using only individuals who went on to intensify with a 3rd add-on treatment, the risk of recording a HbA1c > 58 mmol/mol was 10% lower with sitagliptin than for sulphonylureas: adjusted HR 0.90 (95% CI 0.82 to 0.98). This however, was not true for those individuals who went to have their sitagliptin or sulphonylureas switched i.e. substituted with another treatment. In this instance, the risk for recording a HbA1c > 58 mmol/mol was 17% higher with sitagliptin (HR 1.17 95% CI 1.07 to 1.28).

In the third subgroup analysis, I examined only those who were deemed “adherent” to treatments for the full follow-up period (30 months). This analysis did not suggest a significant difference between sitagliptin and sulphonylureas in the risk of recording a HbA1c > 58 mmol/mol.

The full output for all five analyses results below in Table 10.3 are presented in Appendix G (Supplementary Tables 10A1-10A5) for reference.

Table 10.3 Cox regression analysis for time to first recording of a HbA1c > 58 mmol/mol for individuals aged ≥ 18 years

Model: Sitagliptin vs Sulphonylureas	Unadjusted (HR, 95% CI)	Adjusted for Sex, Age & Baseline HbA1c (HR, 95% CI)	Fully Adjusted Multivariable¥ (HR, 95% CI)
Aged ≥ 18 years			
Parsimonious model (n=23,601)	1.09 (1.05 to 1.14)	1.04 (1.00 to 1.09)	1.11 (1.06 to 1.16)
Clinical model* (n=22,839)	(as above)	(as above)	(as above)
Intensification Population (n=3,654)	0.89 (0.82 to 0.96)	0.89 (0.82 to 0.96)	0.90 (0.82 to 0.98)
Switching Population (n=3,232)	1.14 (1.05 to 1.24)	1.13 (1.04 to 1.23)	1.17 (1.07 to 1.28)
"Adherent" population for 30 months (n=6,846)	0.99 (0.91 to 1.08)	0.93 (0.86 to 1.02)	0.97 (0.89 to 1.06)

*Loss of 762 individuals from cohort used in parsimonious model analysis due to missing Townsend quintile

¥Mutually adjusted for baseline HbA1c, age, year entry, Mean Face to Face Consultation Frequency per year, sex, Townsend quintile, smoking status, history of excessive alcohol intake, heart failure, pancreatitis, and having a prescription within 3 months prior to the index date for diuretics and antidepressant medication.

HR=Hazard Ratio, CI=Confidence Interval.

Note: Individuals prescribed sulphonylureas are the reference population in all regression estimates above.

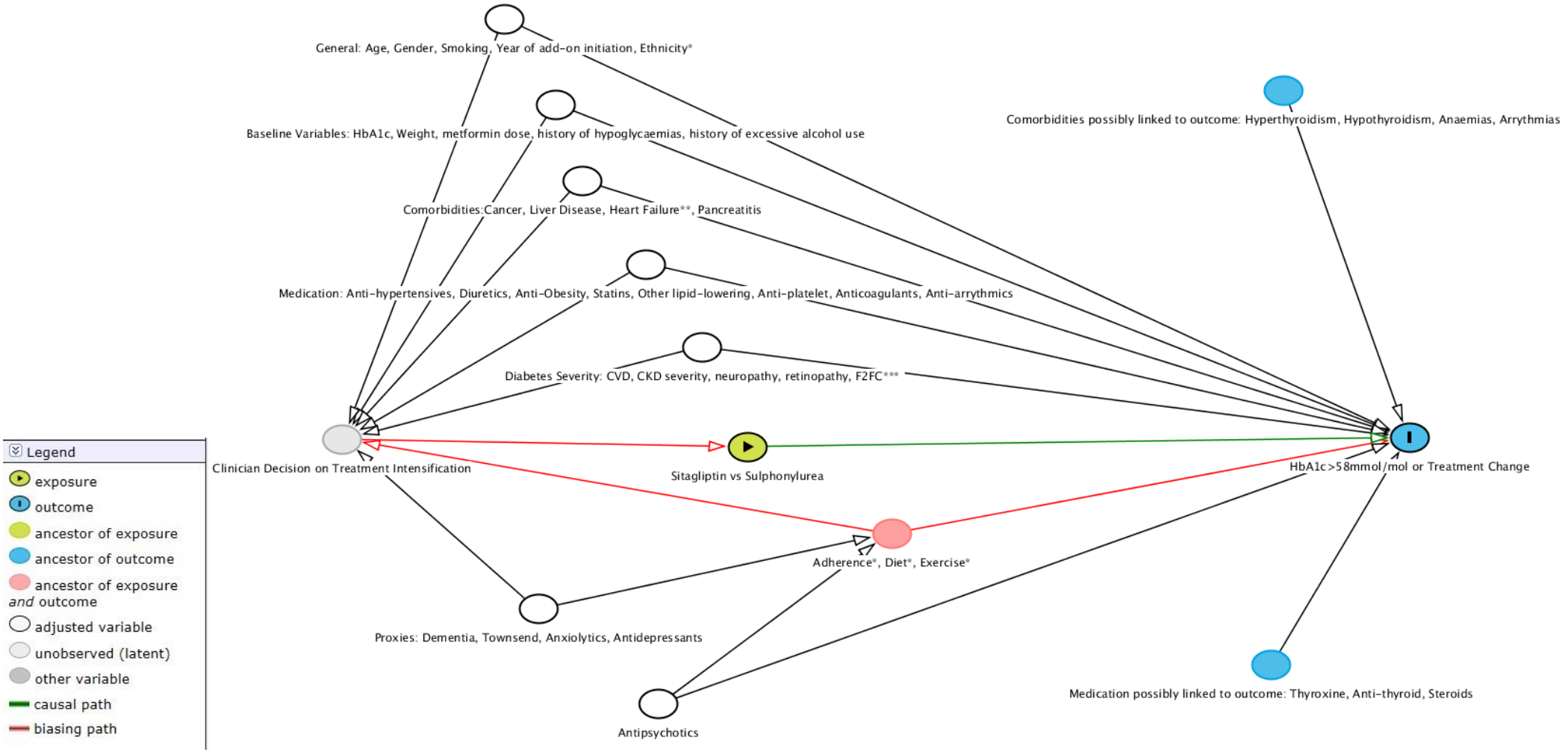


Figure 10.3 Direct Acyclic Graph depicting relationship between covariates, exposure and outcome for clinical model examining time to first recording of a HbA1c > 58 mmol/mol or a treatment change

*Ethnicity though included in DAG was not well recorded in THIN, Adherence, Diet and Exercise not recorded in THIN hence proxies used where possible

**Heart Failure refers to those with either Read code for Heart Failure recorded or on treatment

***Face to Face Consultation Frequency

CVD= Cardiovascular disease, CKD=Chronic Kidney Disease.

Table 10.4 Justifications for confounder selection for clinical model for analysis on time to recording of first HbA1c > 58 mmol/mol and first anti-diabetic treatment change

***A Priori* Confounders (measured at baseline)**	**Exposure Association**	**Outcome Association (with both recording of a HbA1c > 58 mmol/mol and treatment change)**
General		
Age at study entry	Imbalance at baseline - may affect treatment choice	Age may affect glycaemic control
Gender	Imbalance at baseline - may affect treatment choice	Gender may affect glycaemic control
Face to Face Consultation frequency (F2FC)	Imbalance at baseline - may affect treatment choice (sulphonylureas increase risk of hypoglycaemias therefore may want more monitoring)	Intensity of management as reflected in frequency of appointments may affect likelihood of recording of outcome
Metformin dose (<1500mg or >1500mg)	Imbalance at baseline	Will affect glycaemic control
Smoking Status	Imbalance at baseline - causes CVD - may affect prescriber decision	Smoking known to affect glycaemic control
Ethnicity*	Imbalance at baseline - may affect treatment choice	Ethnic variation in glycaemic control exists
Adherence**	History of poor medication adherence may affect prescriber choice of treatment	Poor medication adherence likely to worsen glycaemic control
Diet**	Type of diet at baseline may affect treatment choice – sulphonylureas carry higher risk of hypoglycaemias	Will affect glycaemic control
Exercise**	Level of exercise an individual undertakes may affect treatment choice	Will affect glycaemic control
Year of add-on initiation	Will effect reasons for choice of exposure – guidance on choice of exposure has changed over time	Guidance on intensity of monitoring will affect frequency of measurements which could impact glycaemic control
Baseline Weight	Imbalance at baseline - may affect treatment choice	Will affect glycaemic control
Baseline HbA1c	Imbalance at baseline - may affect treatment choice	Will affect glycaemic control
History of Hypoglycaemias	Imbalance at baseline - may affect treatment choice (sitagliptin favoured over sulphonylureas)	Will affect glycaemic control
History of excessive alcohol use	Prescriber may avoid sulphonylureas as higher risk of hypoglycaemia	Will affect glycaemic control
Comorbidities		
Cancer	Imbalance at baseline - may affect treatment choice	Will affect glycaemic control
Cardiovascular disease (CVD)	Imbalance at baseline - may affect treatment choice	CVD likely to affect glycaemic control
Heart Failure (HF)	Imbalance at baseline - may affect treatment choice as	HF indicative of poor cardiovascular health and

	signal with sitagliptin of worsening HF	likely to affect glycaemic control
Neuropathy	Imbalance at baseline - may affect treatment choice based on perceived diabetes severity and treatment efficacy	Marker of poor glycaemic control
Retinopathy	Imbalance at baseline - may affect treatment choice based on perceived diabetes severity and treatment efficacy	Marker of poor glycaemic control
Chronic Kidney Disease	Imbalance at baseline - may affect treatment choice	Likely to affect glycaemic control
Liver disease	Imbalance at baseline - may affect treatment choice	Likely to affect glycaemic control
Pancreatitis	If have history of pancreatitis – prescriber may favour sulphonylureas (small increased risk of pancreatitis with sitagliptin has been reported)	History of pancreatic dysfunction may increase propensity of erratic glycaemic control
Medications		
Anti-hypertensive	Imbalance at baseline - may affect treatment choice e.g. Ramipril may not be for BP but be marker of future CVD risk and hence affect exposure choice	Marker of poor cardiovascular health which may affect glycaemic control
Diuretics	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor cardiovascular health which may affect glycaemic control
Antiplatelet	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor cardiovascular health which may affect glycaemic control
Anticoagulant	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor cardiovascular health which may affect glycaemic control
Antiobesity	Imbalance at baseline - may affect treatment choice as clinician avoids sulphonylureas	May affect weight which in turn may affect glycaemic control
Statins	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor cardiovascular health which may affect glycaemic control
Other lipid lowering drugs	Imbalance at baseline - may affect exposure choice	Marker of poor cardiovascular health which may affect glycaemic control
Anti-arrythmics	Imbalance at baseline - may affect treatment choice as suggests presence of CVD or CVD risk	Marker of poor cardiovascular health which may affect glycaemic control
Others		
Dementia	Imbalance at baseline - may affect exposure choice as sulphonylureas carry risk of hypoglycaemia	Dementia may act as a weak proxy for adherence to medication and hence glycaemic control

Townsend Quintile	Imbalance at baseline - may affect exposure choice	Higher Townsend quintile (more deprived) – may act as a weak proxy for worse glycaemic control
Anxiolytics	History of anxiety may drive prescriber to avoiding sulphonylureas as carry greater risk of hypoglycaemia	May act as a weak proxy for adherence and thus affect glycaemic control
Antidepressants	History of depression may drive prescriber to avoiding sulphonylureas as carry greater risk of hypoglycaemia	May act as a weak proxy for adherence and thus affect glycaemic control
Variables measured at baseline which may affect outcome but not exposure		
Comorbidities		
Anaemias	None	Will affect oxygen carrying capacity of the blood, circulating red blood cells and in turn possibly HbA1c
Hyperthyroidism	None	Will affect metabolism and thereby glycaemic control
Hypothyroidism	None	Will affect metabolism and thereby glycaemic control
Arrythmias	None	Marker of poor cardiovascular health which may affect glycaemic control
Medications		
Thyroxine	None	Will affect thyroid function and thus glycaemic control
Anti-thyroid drugs	None	Will affect thyroid function and thus glycaemic control
Antipsychotics	None	Several anti-psychotics affect glycaemic control directly
Steroids – Oral/Intravenous	None	Will affect glycaemic control

*Ethnicity though included in DAG was not well recorded in THIN.
**Diet, Adherence and Exercise not recorded in THIN hence proxies used where possible
Note: Any variable that affects glycaemic control will inevitable affects recording of a HbA1c > 58 mmol/mol and in turn the possibility of an anti-diabetic treatment change.

10.5.5 Time to first recording of an anti-diabetic treatment regimen change

10.5.5.1 Graphical evaluation of time to first recording of a treatment regimen change

The Kaplan Meier graph for time to recording of an anti-diabetic treatment regimen change over follow-up is illustrated in Figure 10.4. The plot for individuals initiated on sitagliptin is markedly different to that for individuals initiated on sulphonylureas. It suggests that a higher proportion starting sitagliptin undergo a treatment regimen change compared to those initiating on sulphonylureas.

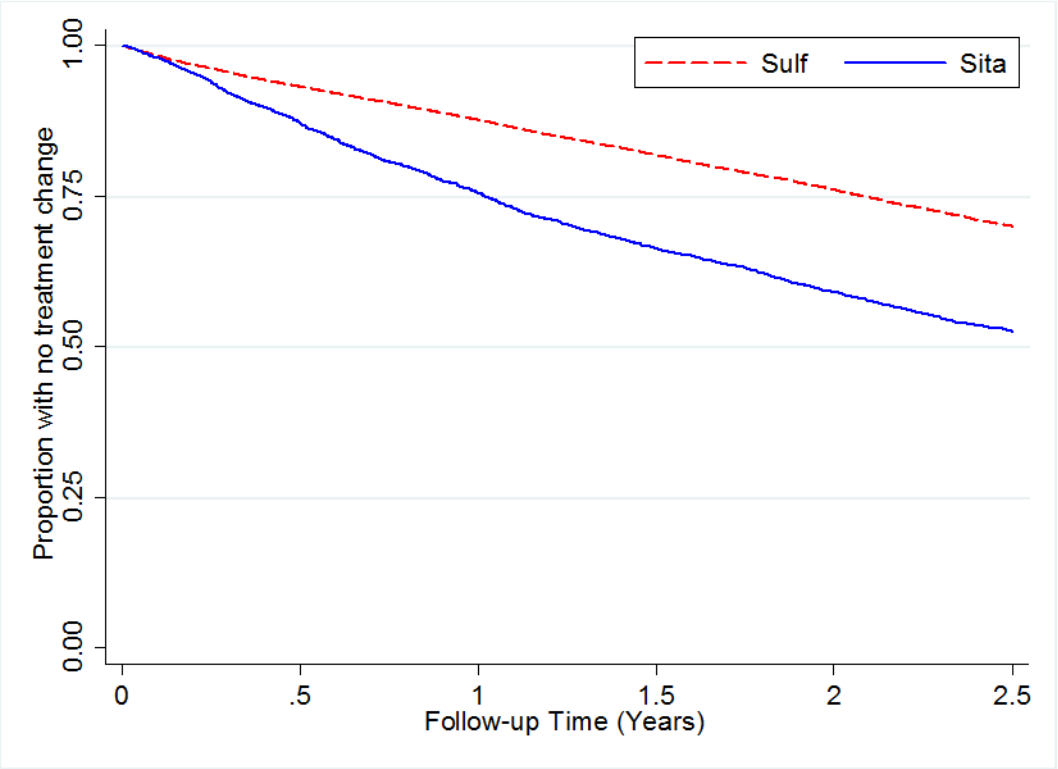


Figure 10.4 Kaplan Meier graph for recording of a treatment regimen change

10.5.5.2 Main analysis

In total, 1,739 (42.1%) individuals of all treated with sitagliptin and 5,147 (26.4%) individuals of all treated with sulphonylureas had an anti-diabetic treatment regimen change recorded during the 30 month study follow-up period. There was significant effect modification by age (log likelihood ratio test for treatment by age interaction, p=0.004). Hence the results below are presented stratified by being aged 18-75 years and aged ≥ 75 years.

10.5.5.2.1 Cohort with individuals aged 18-75 years

Individuals aged 18-75 years prescribed sitagliptin as add-on compared to sulphonylureas had a 84% higher risk of recording an anti-diabetic treatment regimen change before adjustment, Hazard Ratio 1.84 (95% CI 1.74 to 1.95), as shown in Table 10.5. After adjustment for baseline HbA1c, sex, age and other covariates identified for inclusion in the parsimonious model, this risk increased further; HR 1.98 (95% CI 1.86 to 2.10). This suggested that those prescribed sitagliptin were almost twice as likely to record a treatment regimen change over the study period of 30 months compared to those prescribed sulphonylureas. The results for the clinical model were consistent with these findings. The Direct Acyclic Graph in Figure 10.4 details the confounders included in this analysis model. The justification for their selection was provided in detail earlier in Table 10.5.

In the subgroup of individuals who ultimately intensified with third-line add-on treatment, the risk of recording a treatment change was found to be 36% higher with sitagliptin compared to sulphonylureas (HR 1.36 95% CI 1.25 to 1.48). However, no difference was detected in risk among those who ultimately switched treatments (not intensified with third-line treatment).

Finally, in the third subgroup analysis among those who were deemed "adherent" for 30 months to the respective treatments, the risk of recording a treatment change was over 2-fold higher among sitagliptin initiators; HR 2.16 (95% CI 1.90 to 2.45) (Table 10.5).

10.5.5.2.2 Cohort with individuals aged ≥ 75 years

The individuals aged ≥ 75 years (n=2,847) had an even higher risk for recording a treatment regimen change with sitagliptin compared to sulphonylureas; HR 2.56 (95% CI 2.03 to 3.23) (Table 10.5). These findings were consistent with those from the clinical model.

Among the subgroup who ultimately intensified treatment, the risk of recording a treatment regimen change was higher with sitagliptin (HR 1.61 95% CI 1.08 to 2.42), while no difference was detected among those who switched. Finally, in the subgroup of those who were deemed "adherent" for 30 months, the Hazard Ratio was 2.44 (95% CI 1.45 to 4.10) (Table 10.5).

The full results from all analyses presented in Table 10.5 are included in Appendix G (Supplementary Tables 10A6-10A15) for reference.

Table 10.5 Cox regression analysis for time to first recording of an anti-diabetic treatment regimen change in individuals aged 18-75 years and aged ≥ 75 years

Model: Sitagliptin vs Sulphonylureas	Unadjusted, (HR, 95% CI)	Adjusted for Sex, Age & Baseline HbA1c (HR, 95% CI)	Fully Adjusted Multivariable (HR, 95% CI)
Aged 18– 75 years			
Parsimonious model (n=20,754)	1.84 (1.74 to 1.95)	1.77 (1.67 to 1.87)	1.98 (1.86 to 2.10)
Clinical model* (n=20,057)	As above	As above	1.99 (1.87 to 2.12)
Intensification Population (n=3,654)	1.44 (1.34 to 1.56)	1.44 (1.33 to 1.55)	1.36 (1.25 to 1.48)
Switching Population (n=3,232)	1.11 (1.02 to 1.20)	1.10 (1.02 to 1.19)	1.08 (0.99 to 1.18)
"Adherent" population for 30 months (n=6,085)	1.95 (1.74 to 2.20)	1.88 (1.67 to 2.11)	2.16 (1.90 to 2.45)
Aged ≥75 years			
Parsimonious model (n=2,847)	2.48 (1.99 to 3.08)	2.45 (1.97 to 3.05)	2.56 (2.03 to 3.23)
Clinical model** (n=2,782)	2.51 (2.01 to 3.14)	2.49 (1.99 to 3.10)	2.63 (2.07 to 3.34)
Intensification Population (n=187)	1.67 (1.18 to 2.37)	1.66 (1.17 to 2.35)	1.61 (1.08 to 2.42)
Switching Population (n=277)	1.04 (0.78 to 1.39)	1.09 (0.82 to 1.46)	1.04 (0.76 to 1.43)
"Adherent" population for 30 months (n=761)	2.29 (1.40 to 3.76)	2.26 (1.38 to 3.71)	2.44 (1.45 to 4.10)

*Loss of 697 individuals from cohort used in parsimonious model analysis due to missing Townsend quintile
**Loss of 65 individuals from cohort used in parsimonious model analysis due to missing Townsend quintile
HR=Hazard Ratio, CI=Confidence Interval
Note: Individuals prescribed sulphonylureas are the reference population in all regression estimates above.

10.5.5.3 Choice of Treatment Augmentation

In total, 1,739 (42.1%) of all individuals treated with sitagliptin and 5,147 (26.4%) of all individuals treated with sulphonylureas had a treatment regimen change recorded during the 30 month study follow-up period.

Of these individuals, 869 (50.0%) of 1,739 individuals treated with sitagliptin and 2,785 (54.1%) of 5,147 individuals treated with sulphonylureas were intensified with third-line treatment during follow-up. Those prescribed sitagliptin were most commonly intensified further with sulphonylureas (693, 79.8%) or thiazolidinediones (79, 9.1%) as shown in Table 10.6. In the case of individuals prescribed metformin and sulphonylureas, 3rd line intensification was most commonly undertaken with a gliptin (1,515, 54.4%) or a thiazolidinedione (650, 23.3%).

Table 10.6 Medications used for third-line treatment intensification

Choice of Treatment Intensification, n(%)	Sitagliptin Group	Sulphonylurea Group
Gliptin*	NA	1,515 (54.4)
Sulphonylureas	693 (79.8)	NA
Insulin	10 (1.1)	282 (10.2)
Acarbose	0 (0)	4 (0.1)
GLP-1 Analogues	49 (5.6)	262 (9.4)
Thiazolidinediones	79 (9.1)	650 (23.3)
SGLT-2 Inhibitors	34 (3.9)	29 (1.0)
Meglitinides	4 (0.4)	9 (0.3)
Other Oral Combination Therapy*	0 (0)	34 (1.2)
Total Intensified, (N)	**869**	**2,785**

*Oral Combination therapies include either metformin and gliptin combinations or metformin and thiazolidinedione combinations
N=Total number of individuals who intensified treatment

Of the individuals who recorded a treatment change during follow-up, 870 (50.0%) of 1,739 individuals treated with sitagliptin and 2,362 (45.9%) of 5,147 individuals treated with sulphonylureas were switched to an alternate anti-diabetic treatment. When it came to switching individuals from a gliptin to another treatment, clinicians chose sulphonylureas (422, 48.5%) and GLP-1 Analogues most commonly (191, 22.0%) as shown in Table 10.7. For switching from a sulphonylurea, clinicians switched to gliptins (1,099, 46.5%) and insulin most commonly (473, 20.0%).

Table 10.7 Medications used for when switching treatment from sitagliptin or sulphonylureas

Choice of Treatment Switch, n(%)	Sitagliptin Group	Sulphonylurea Group
Gliptin*	101 (11.6)	1,099 (46.5)
Sulphonylureas	422 (48.5)	NA
Insulin	40 (4.6)	473 (20.0)
Acarbose	0 (0)	3 (0.1)
GLP-1 Analogues	191 (22.0)	131 (5.5)
Thiazolidinediones	67 (7.7)	416 (17.6)
SGLT-2 Inhibitors	35 (4.0)	31 (1.3)
Meglitinides	4 (0.4)	37 (1.6)
Other Oral Combination Therapy**	10 (1.2)	172 (7.3)
Total Switched, (N)	**870**	**2,362**

*For sitagliptin, this includes gliptins other than sitagliptin (saxagliptin, linagliptin, alogliptin, vildagliptin)
**Oral Combination therapies include either metformin and gliptin combinations or metformin and thiazolidinedione combinations
N=Total number of individuals who switched treatment

10.5.6 Descriptive Analysis to assess clinician response to recording of a HbA1c > 58 mmol/mol among those initiated on sitagliptin or sulphonylureas

In this section, I bring the results from both cohort studies described in this chapter together to try and investigate why those prescribed sitagliptin were almost twice as likely to record a treatment change compared to sulphonylurea initiators, however only 11% more likely to record a HbA1c > 58 mmol/mol.

There were 2,695 (65.3%) individuals treated with sitagliptin and 12,476 (64.0%) individuals treated with sulphonylureas who had a record of HbA1c >58 mmol/mol during the study follow-up period of 30 months as detailed in Section 10.5.4.2. Of these individuals with a HbA1c recording > 58 mmol/mol, 1,789 (66.4%) prescribed sitagliptin and 10,446 (83.7%) prescribed sulphonylureas had no treatment change introduced within 3 months of this recording (Table 10.8).

Table 10.8 Analysis of individuals with a HbA1c recording > 58 mmol/mol who had their treatment changed

Add-on Treatment	No. with HbA1c > 58 mmol/mol recorded (N)	Treatment changed before HbA1c > 58 mmol/mol, n(%)	Treatment changed within 3 months of HbA1c > 58 mmol/mol, n(%)	Treatment not changed within 3 months, n(%)
Sita	2,695	290 (10.8)	616 (22.8)	1,789 (66.4)
Sulf	12,476	879 (7.0)	1,151 (9.3)	10,446 (83.7)

N=Total number of individuals with HbA1c > 58 mmol/mol recorded and is the denominator used across rows.
Sita=sitagliptin, sulf=sulphonylureas.

Among those individuals that did not have their treatment changed despite the recording of a HbA1c > 58 mmol/mol, dose changes were then analysed. In total, 10 (0.6%) individuals prescribed sitagliptin and 1,806 (17.3%) individuals prescribed sulphonylureas had an increase in dosage prescribed within 3 months of recording a HbA1c > 58 mmol/mol (Table 10.9). This indicated that individuals prescribed sulphonylureas more commonly had their dose increased after this HbA1c recording.

Table 10.9 Analysis of medication dosage changes within 3 months of a HbA1c recording > 58 mmol/mol among individuals who did not have their treatment changed

Add-on Treatment	Treatment not changed within 3 months, (N)	Stopped add-on, n(%)	Increased Dose, n(%)	No dose change, n(%)	Decreased Dose, n(%)	Dosing Info not obtainable n(%)
Sita	1,789	145 (8.1%)	10 (0.6%)	1,633 (91.3%)	2 (0.1%)	0 (0)
Sulf	10,446	701 (6.7%)	1,806 (17.3%)	7,592 (72.6%)	340 (3.3%)	7 (0.1%)

N=Total number of individuals with HbA1c > 58 mmol/mol recorded with no treatment change within 3 months and is the denominator used across rows.
Info=Information, sita=sitagliptin, sulf=sulphonylureas.
Note: Where dosing information was not recorded in THIN, the dose was calculated manually based on quantity issued and duration of the prescription where this was available.

10.6 Discussion

10.6.1 Key Findings

In this chapter, I found that individuals prescribed sitagliptin had a 11% higher risk of recording a HbA1c > 58 mmol/mol compared to individuals prescribed sulphonylureas over 30 months of follow-up (HR 1.11 95% CI 1.06 to 1.16). A HbA1c > 58 mmol/mol is indicative of poor glycaemic

control and NICE and most international guidelines recommend treatment change at this point for the majority of individuals.[22] The analysis into time to treatment change revealed that treatment change was almost twice as likely with sitagliptin compared to sulphonylureas over the 30 months (HR 1.98 95% CI 1.86 to 2.10). This risk was even higher for those aged ≥ 75 years (HR 2.56 95% CI 2.03 to 3.23).

Therefore, in total, though the rate of recording of a HbA1c > 58 mmol/mol was higher by 11% in the sitagliptin cohort, treatment change was 98% higher. This finding was then analysed in greater detail.

In an analysis examining only those who had a recording of HbA1c > 58 mmol/mol, inertia for treatment change was found to exist in both groups, but was highest for individuals prescribed sulphonylureas. In total, 1,789 (66.4%) individuals prescribed sitagliptin and 10,446 (83.7%) individuals prescribed sulphonylureas as add-on to metformin had no treatment change introduced within 3 months of recording this undesirable HbA1c > 58 mmol/mol despite NICE recommendations advocating change.[22] A more in depth analysis of dose changes among those individuals where no treatment was changed, revealed that 1,806 (17.3%) individuals of those prescribed sulphonylureas had the dose increased in response to the HbA1c > 58 mmol/mol, however this occurred in only 10 (0.6%) individuals prescribed sitagliptin. This could be explained by the fact that sitagliptin is usually started at maximum licensed dosage when prescribed, unlike sulphonylureas which needs gradual titration from a lower dose usually with the aid of capillary blood glucose measurements.

Thus, in summary, despite a similar risk of recording a HbA1c > 58 mmol/mol after initiation with either sitagliptin or sulphonylureas, clinicians were found to be more prepared to introduce an anti-diabetic regimen change for individuals prescribed sitagliptin. This may be partly explained by the fact that clinicians opted to increase dosage in certain instances with sulphonylureas rather than introduce a new treatment when the HbA1c was above an undesirable 58 mmol/mol. These findings will be discussed in further detail in Chapter 11.

10.6.2 Handling Missing Data

The main reason for loss of individuals for analysis from our initial cohort was due to the absence of some baseline data though in general, this was very well recorded with only 8.3% missing. To investigate those missing data, I undertook an in depth analysis comparing the complete cohort used for analysis to the cohort missing recording for a HbA1c between 3-30 months after the index date and cohort missing some baseline data. This is recommended good practice when

investigating the impact of missing data on analyses.[172,173] The results of these analyses showed that the characteristics of the individuals prescribed sitagliptin and sulphonylureas across these three groups: cohort with complete data, cohort with missing outcome data and cohort missing some baseline data were highly similar and exhibited little variation.

Analysis of the outcome for "time to first recording of a HbA1c > 58 mmol/mol" relied on the frequency of recording of HbA1c being similar across both sitagliptin and sulphonylurea cohorts (i.e. individuals prescribed sitagliptin and sulphonylurea must have an equal chance of having a HbA1c recorded at any timepoint after the index date, be that > 58 mmol/mol or ≤ 58 mmol/mol). This was shown to indeed, be true in Chapter 7 (Section 7.4.2.1). This challenge with recording bias was not an issue for the outcome "time to treatment change", as the new medication is either prescribed or not prescribed.

10.7 Context of this chapter in overall work

In this chapter I have presented the result from two cohort studies undertaken for this thesis, examining time to first recording of a HbA1c > 58 mmol/mol and then time to first treatment change respectively after add-on of sitagliptin or sulphonylureas to metformin. In Chapter 11, I will place my findings in the context of existing literature, highlight the strengths and limitations of this work, and also describe the implications of these findings for clinical practice, public health and future research.

Chapter 11 Discussion

11.1 Chapter Overview

In this chapter, I will place the findings of this thesis, focusing on those from the cohort studies described in Chapters 9 and 10 within the context of the existing literature. I will also detail the strengths and limitations of these studies as well as the main clinical and research implications of the findings. I have already discussed the implications of the diabetes algorithm described in Chapter 4 and the study exploring trends in incidence, prevalence and prescribing of type 2 diabetes mellitus (T2DM) in Chapter 5 in depth. Hence, these will only be briefly summarised here. The main purpose of these early studies was to lay the foundation for undertaking the primary aim of this thesis: to explore the effectiveness of sitagliptin compared to sulphonylureas as add-on to metformin.

11.2 Summary of key findings

This thesis evaluates the effectiveness of sitagliptin compared to sulphonylureas among individuals with T2DM as add-on to metformin across 4 domains:

1) Glycaemic control as measured by comparative change in HbA1c from baseline approximately 12 months after initiation

2) Weight control as measured by comparative change in weight from baseline approximately 12 months after initiation

3) Time before first recording of a undesirable HbA1c > 58 mmol/mol

4) Time before first recording of an anti-diabetic treatment change (prescribing of an alternate anti-diabetic treatment)

I first generated an algorithm to identify individuals with T2DM in UK primary care electronic databases (Chapter 4). I then used this algorithm to create a cohort of individuals with T2DM in THIN and examined the incidence and prevalence of T2DM between 2000 and 2013 (Chapter 5). I found that the incidence of T2DM rose significantly between 2000 and 2005, after which it stabilised around 3.99 per 1000 PYAR in men and 3.73 per 1000 PYAR in women by 2013. Equally the point prevalence of T2DM rose from 2.39% in the year 2000 to 5.32% by 2013. I then focused on a cohort of individuals prescribed sitagliptin or sulphonylureas as add-on to metformin (Chapters 6-8), identifying potential confounders to control for in my cohort studies through two distinct approaches: 1) data driven associations and 2) *a priori* agreed theoretical associations determined using Direct Acyclic Graphs (DAGs).

In the first cohort study examining comparative change in HbA1c from baseline, I found that the HbA1c approximately 12 months after baseline was on average 0.89 mmol/mol (95% CI 0.33 to 1.45) higher when sitagliptin was added to metformin instead of sulphonylureas for adults aged ≥ 18 years (including those aged ≥ 75 years). This indicated a statistically smaller reduction in HbA1c after 12 months with sitagliptin of close to 1 mmol/mol. However, it was clinically of little importance as this represents a negligible difference in glycaemic control.

In the second cohort study, I found a significant statistical and clinical reduction in weight, 12 months after baseline, with sitagliptin compared to sulphonylureas of -2.26 kg (95% CI -2.48 to -2.04) in individuals aged 18-75 years. This difference was driven by an approximately 1.4kg weight gain observed with those initiated on sulphonylureas and approximately 1.4kg weight loss with those prescribed sitagliptin. A smaller -1.31kg (95% CI -1.96 to -0.66) comparative weight difference was observed among older individuals aged ≥ 75 years. This was because no weight gain with sulphonylureas was observed in this older cohort.

The third cohort study showed a 11% higher risk of recording a HbA1c > 58 mmol/mol among all individuals aged ≥ 18 years (including those aged ≥ 75 years) prescribed sitagliptin compared to those prescribed sulphonylureas [Hazard Ratio (HR) 1.11 95% CI 1.06 to 1.16]. This indicated the treatments were similar in achieving glycaemic targets over the 30 months of follow-up examined. This threshold of 58 mmol/mol is one above which NICE recommends treatment change.[22]

The fourth and final cohort study revealed that those prescribed sitagliptin were almost twice as likely to record an anti-diabetic treatment regimen change compared to those prescribed sulphonylureas (HR 1.98 95% CI 1.86 to 2.10). This risk was even higher for those aged ≥ 75 years (HR 2.56 95% CI 2.03 to 3.23). This finding prompted further investigation, as this higher rate of treatment change was unusual given that the recording of a HbA1c > 58 mmol/mol was only 11% higher with sitagliptin.

I then examined only those individuals that had a recording of a HbA1c > 58 mmol/mol during 30 months of follow-up, which included 2,695 individuals prescribed sitagliptin and 12,476 prescribed sulphonylureas. I found that 1,789 (66.4%) of those prescribed sitagliptin and 10,446 (83.7%) of those prescribed sulphonylureas had no treatment change introduced within 3 months of recording a HbA1c > 58 mmol/mol (despite NICE guidance advocating this). This suggested a significant inertia in treatment change which was greater with sulphonylureas. Among those that had no treatment change introduced, 1,806 (17.3%) of those prescribed sulphonylureas did have

their prescribed dose increased in response to the recording of a HbA1c > 58 mmol/mol. Only 10 (0.6%) of those prescribed sitagliptin, however had their dose increased.

11.3 Comparison with existing literature

The clinical findings from the four cohort studies presented in Chapters 9 and 10 will now be put in the context of existing literature below.

11.3.1.1 Change in HbA1c from baseline with sitagliptin vs sulphonylureas

A comparison of my retrospective observational study examining comparative change in HbA1c from baseline for sitagliptin vs sulphonylureas as add-on to metformin, with other previous studies is illustrated in Figure 11.1. This figure was first presented in Chapter 2 (Section 2.4.4, Figure 2.2), where I described the systematic review that explored the effectiveness of sitagliptin compared to sulphonylureas as add-on to metformin. For Figure 11.1, I have now added my completed study to the forest plot. The meta-analysis summary estimate presented in Figure 11.1 suggested no significant difference between sitagliptin and sulphonylureas (0.54 mmol/mol 95% CI -0.28 to 1.35 mmol/mol). These results were in line with my study which found no clinically significant difference in HbA1c after approximately 12 months from baseline (0.89 mmol/mol 95% CI 0.33 to 1.45 mmol/mol). This is because an approximate 1mmol/mol difference would not impact on an individual's short or longer-term prognosis for glycaemic control as it is so low in magnitude. Unlike the trials included in the meta-analysis estimate, the data included in my cohort study was directly from individuals seen in clinical practice and collected during routine usage of the treatments, Hence, this should give a more accurate reflection of "real world" effectiveness (provided confounding is correctly controlled for). My study is the largest study that has been undertaken to date examining this research question, hence the greater precision seen in the estimate.

Only one other observational study by Suraj et al was suitable for inclusion in Figure 11.1.[62] This was prospective and set in a single tertiary care facility in India. The follow-up time in this study was 3 months only and the total population was 100. This study suggested a significantly greater reduction in HbA1c from baseline with sulphonylureas compared to sitagliptin of 5.3 mmol/mol. However, due to the short duration of this study it is possible both treatments were not given sufficient time to have full effect. Additionally, the study population was considerably smaller than in my study and they did not adjust for any baseline factors relating to demographics, HbA1c and comorbidities which may also have biased their final results.

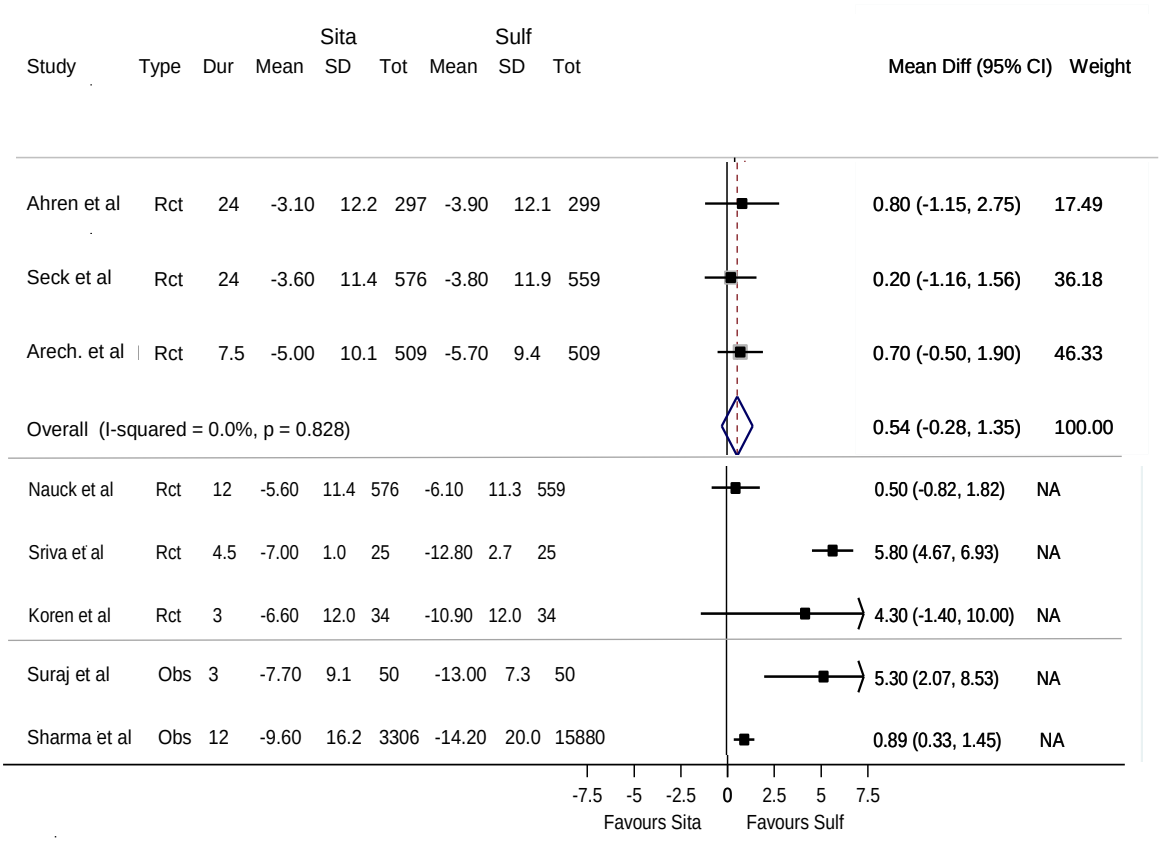


Figure 11.1 Forest plot (including subgroup meta-analysis) comparing this study with previous studies examining HbA1c (mmol/mol) change between sitagliptin and sulphonylureas as add-on to metformin

Rct=Randomized controlled trial, Obs=Observational study, Dur=duration in months, SD=Standard deviation, Tot=total participants, Mean Diff=mean difference, OR=Odds ratio, NA=not applicable, Sita=Sitagliptin, Sulf=sulphonylureas, Arech= Arechavaleta, Sriva=Srivastava.
Note: Weights where present are from fixed effects meta-analysis though random-effects estimates were identical.

At the time my study was commenced, there was no study examining the effectiveness from a glycaemic point of view of sitagliptin compared to sulphonylureas as add-on to metformin in older individuals aged ≥ 75 years. Since then a randomised controlled trial conducted in Japan by Terauchi et al in 2017, has shown similar glycaemic change with sitagliptin compared to a sulphonylureas in 272 individuals aged ≥ 60 years, 12 months after initiation (1.2 mmol/mol, 95% CI -0.2 to 2.6).[174] The mean age of the 272 individuals was 70.5 with a standard deviation of 5.5 years, hence most were younger than in my cohort. Additionally, the individuals included were either on no other treatment, α-glucosidase inhibitor or metformin before add-on, unlike in my study, where all were required to be prescribed metformin at baseline.[174] Nevertheless, the results obtained were comparable to my finding of no clinically significant difference between both treatments in 2,305 individuals (266 on sitagliptin and 2,039 on sulphonylureas) analysed aged ≥ 75 years.

A post-hoc pooled subgroup analysis of older adults aged ≥ 65 years from 3 previously completed randomised controlled trials was published by Shankar et al in 2015.[43] This included 372 individuals (178 prescribed sitagliptin and 194 prescribed sulphonylureas) as add-on to metformin or diet-control. Interpretation of these findings is complicated by the fact that the sample pooled included two groups, firstly individuals who were on single therapy with sitagliptin or sulphonylureas, and secondly, individuals on dual therapy with one of these and metformin. Furthermore, the sample included few individuals aged ≥ 75 years. For example, the largest of the three contributing sub-studies led by Nauck et al excluded individuals aged ≥ 78 years.[56] Nevertheless, no significant difference between sitagliptin and sulphonylureas in terms of HbA1c was evident, with a similar HbA1c reduction of approximately 7.7 mmol/mol (0.7%) in both arms. In my "real world" cohort of older adults, I observed a larger reduction of 9.6 mmol/mol (0.88%) and 13.7 mmol/mol (1.25%) with sitagliptin and sulphonylureas respectively. However, after adjustment for baseline differences, no clinically significant difference in HbA1c reduction between treatments was observed.

11.3.1.2 Change in weight from baseline with sitagliptin vs sulphonylureas

A comparison of my retrospective observational study examining comparative change in weight from baseline for sitagliptin vs sulphonylureas as add-on to metformin, with other previous studies is illustrated in Figure 11.2. This forest plot, has been updated from Chapter 2 (Section 2.4.5, Figure 2.2) to include my completed study for comparison.

The meta-analysis summary estimate presented in Figure 11.2 suggested a statistically significant reduction in weight with sitagliptin from baseline when compared to sulphonylureas -2.05 kg (95% CI -2.38 to -1.71). I found a similar comparative weight reduction approximately 12 months after initiation with sitagliptin among individuals aged 18-75 years of -2.26 kg (95% CI -2.48 to -2.04). This comparative reduction observed was driven by a mean weight gain of close to 1.4 kg observed in the sulphonylureas group and a mean weight loss of close to 1.4kg observed in the sitagliptin group. Though a comparative difference of 2.26 kg may not appear large in magnitude, a difference of this size has been shown to correlate with better clinical outcomes relating to physical and mental health.[72]

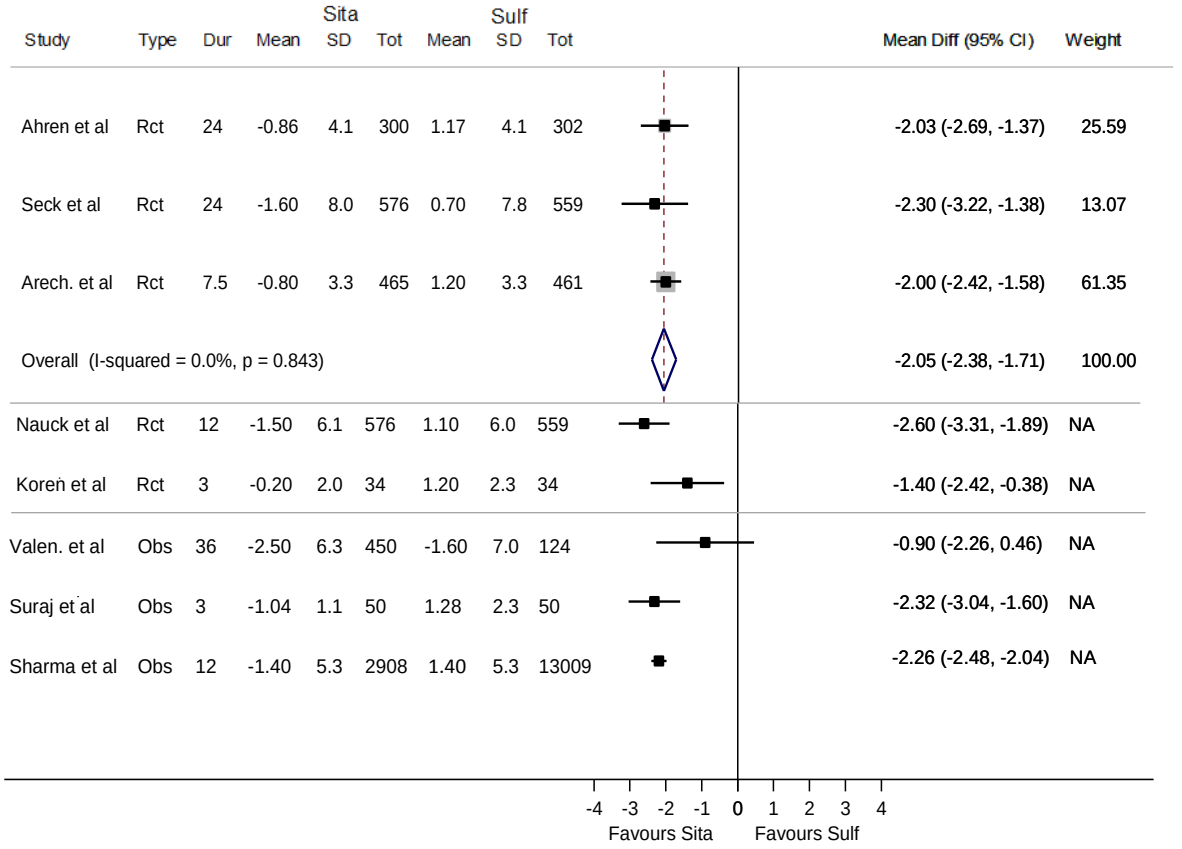


Figure 11.2 Forest plot (including subgroup meta-analysis) comparing my study (adults aged 18-75 years only) with previous studies examining weight (kg) change between sitagliptin and sulphonylureas as add-on to metformin
Rct=Randomized controlled trial, Obs=Observational study, Dur=duration in months, SD=Standard deviation Tot=total participants, Mean Diff=mean difference, NA=not applicable, Sita=Sitagliptin, Sulf=sulphonylureas, Arech=Arechavaleta, Valen=Valensi.
Note: Weights where present are from fixed effects meta-analysis though random-effects estimates were identical.

Two observational studies reported changes in weight from baseline with sitagliptin compared to sulphonylureas.[62,63] One of these studies led by Valensi et al was 36 months in duration, prospective in nature and deemed to be of high methodological quality in my appraisal in Chapter 2 (Section 2.4.2).[63] This study suggested that following longer follow-up of 36 months, no significant weight differences were observed between those initiated on sitagliptin compared to sulphonylureas. It is possible therefore, that any comparative reduction observed does dissipate with time. The other study led by Suraj et al also detected a significant comparative weight reduction of around -2.32kg (95% CI -3.04 to -1.60) with sitagliptin. However as detailed earlier in Chapter 2 (Section 2.4.2), there were several deficiencies in this study relating to controlling for confounding.[62]

My study included 2,106 individuals (252 on sitagliptin and 1,854 on sulphonylureas) aged ≥ 75 years at time of initiation of add-on treatment. I found a significant comparative weight reduction among individuals aged ≥ 75 years initiated on sitagliptin compared to sulphonylureas of -1.31 kg (95% CI -1.96 to -0.66). This was notably lower in magnitude than that observed in those aged 18-75 years due to no observed weight gain in the sulphonylurea group. Terauchi et al in 2017 reported similar findings in a trial of 272 participants aged ≥ 60 years. They found a decrease in weight of approximately 1kg with sitagliptin in their study and no weight gain with sulphonylureas as in my study, though their cohort was younger and smaller in size.[174] A larger comparative weight loss of 2.2 kg was observed with sitagliptin compared to sulphonylureas in the pooled study published by Shankar et al. However as detailed earlier, this study also included individuals who were younger in age than in my study and individuals not prescribed metformin.

11.3.1.3 Time to first recording of a HbA1c > 58 mmol/mol

Several studies have examined the proportion of individuals on sitagliptin vs sulphonylureas achieving the lower glycaemic target of < 53 mmol/mol by study end as illustrated in Figure 11.3. This meta-analysis indicated no significant difference between treatments, as did results for the other studies which were too heterogenous to be included for meta-analysis. A similar plot detailing three studies which reported the proportion achieving a HbA1c < 48 mmol/mol by end of study is presented in Figure 11.4. This also found no significant difference between treatments.

In my cohort study, I set a more liberal, and clinically realistic HbA1c threshold of 58 mmol/mol to evaluate if a treatment had been able to maintain glycaemic control. This threshold has been set by the National Institute for Health and Care Excellence (NICE) as the cut-off above which treatment change should be considered usually by means of intensification. A switch to another medication is recommended however, if a particular therapy is not being tolerated by the individual or the individual is non-adherent to their prescribed regimen.[22] A target of < 48 mmol/mol in particular examined in the RCTs, is quite unrealistic in “real world” practice and could place many individuals, particularly older adults at too great a risk of hypoglycaemia.[22]

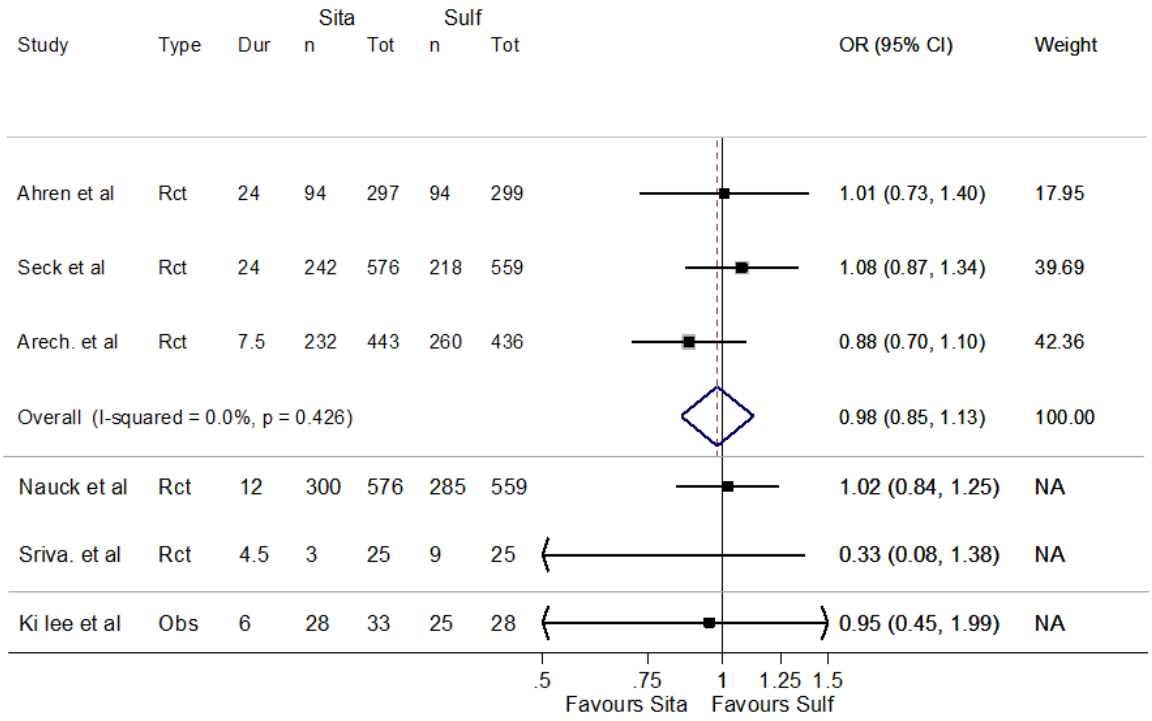


Figure 11.3 Forest plot (including sub-group meta-analysis) comparing sitagliptin and sulphonylureas for proportions achieving a HbA1c< 53mmol/mol (< 7%) at end of study.
Rct=Randomized controlled trial, Obs=Observational study, Dur=duration in months, SD=Standard deviation, Tot=total participants, OR=Odds ratio, NA=not applicable, Sita=Sitagliptin, Sulf=sulphonylureas, Arech=Arechavaleta, Sriva=Srivastava.
Note: Weights where present are from fixed effects meta-analysis though random-effects estimates were identical

Of the 23,601 individuals analysed for risk of recording of a HbA1c > 58 mmol/mol in my study, 15,171 (64.3%) of the cohort failed to maintain a HbA1c below this desirable threshold. This included 2,695 (65.3%) individuals treated with sitagliptin and 12,476 (64.0%) individuals treated with sulphonylureas. I found that all individuals aged ≥ 18 years who were prescribed sitagliptin as add-on were only 11% more likely to record a HbA1c > 58 mmol/mol over 30 months of follow-up [HR 1.11 (95% CI 1.06 to 1.16)] than those prescribed sulphonylureas. These findings indicated that both treatment were equally effective in achieving glycaemic targets.

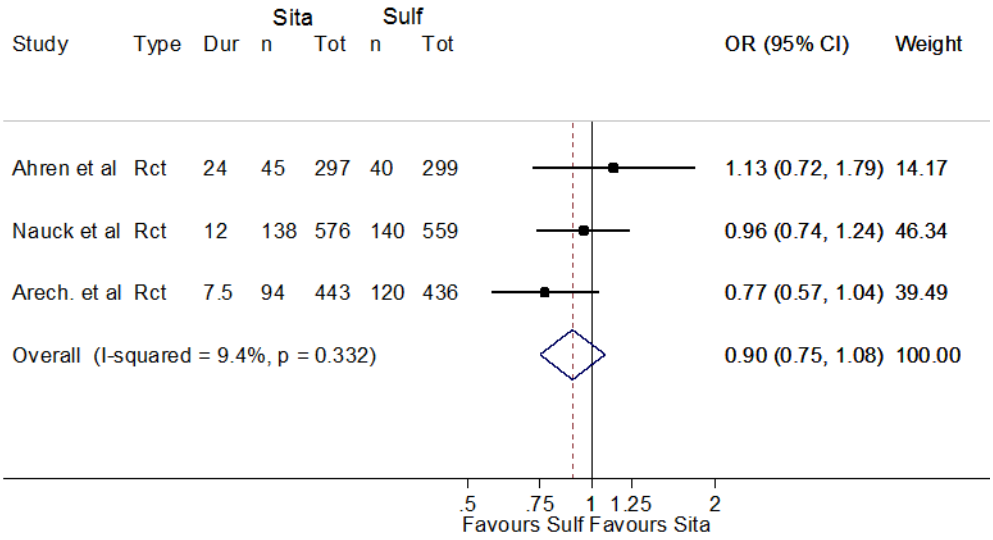


Figure 11.4 Forest plot comparing sitagliptin and sulphonylureas for proportions achieving a HbA1c < 48mmol/mol (< 6.5%) at end of study
Rct=Randomized controlled trial, Dur=duration in months, SD=Standard deviation, Tot=total participants, OR=Odds ratio, NA=not applicable, Sita=Sitagliptin, Sulf=sulphonylureas, Arech= Arechavaleta.
Note: weights where present are from fixed effects meta-analysis though random-effects estimates were identical.

11.3.1.4 Time to first recording of an anti-diabetic treatment regimen change

In my fourth and final cohort study, I found that those individuals aged 18-75 years prescribed sitagliptin were almost twice as likely to have an anti-diabetic treatment regimen change recorded than those prescribed sulphonylureas (HR 1.98 95% CI 1.86 to 2.10), over 30 months of follow-up. An even higher rate of treatment change was observed in individuals aged ≥ 75 years (HR 2.56 95% CI 2.03 to 3.23). Only one other completed prospective cohort study led by Valensi et al explored the risk of needing an anti-diabetic treatment change between those initiated on sitagliptin and sulphonylureas as add-on to metformin. This study had a longer follow-up period of 36 months and found that the adjusted risk of needing treatment change was in fact lower with sitagliptin: (HR 0.65 95% CI 0.57 to 0.73).[63]

Though the study led by Valensi et al was designed to simulate everyday clinical practice as well, the study protocol did require documentation of clinical findings at recommended 3 monthly intervals in accordance with clinical guidelines in France.[63] Furthermore, the mean baseline HbA1c of both the sitagliptin and sulphonylurea groups was 60 mmol/mol and 58 mmol respectively with over 30% recording a HbA1c < 58 mmol/mol at the beginning of the study, indicating excellent glycaemic control at baseline. In my cohort study, I had a considerably higher mean baseline HbA1c of 70.9 mmol/mol and 75.0 mmol/mol for sitagliptin and sulphonylureas

respectively, indicative of significantly worse baseline glycaemic control and more typical of "real world" patients. I also analysed a larger cohort (n=1,354 in Valensi et al vs n=23,601 in my study). Anti-diabetic treatment change is recommended in response to inadequate glycaemic control, individual intolerance to medication or individual non-adherence to a particular medication.[175] Inadequate glycaemic control usually being the most common cause. Of the 23,601 individuals I analysed earlier for risk of recording of a HbA1c >58 mmol/mol in this study, 15,171 (64.3%) of the cohort failed to maintain a HbA1c below this desirable threshold over 30 months. In contrast, in the study led by Valensi et al almost 60% had a HbA1c < 53 mmol/mol by study end, further highlighting significantly better glycaemic control in this cohort overall.[63] Thus in Valensi et al, a lower mean baseline HbA1c and the protocol-driven requirement for more detailed documentation during 3-monthly follow-up may have led to participation of individuals with better glycaemic control, better self-motivation to control the T2DM but also in turn a lower likelihood of inertia for treatment change – an inertia which is highly evident in my study. This may account for such contrasting findings between Valensi et al and my study. Further possible explanations as to why the risk of treatment change was higher with sitagliptin in my study, will be outlined in the next section

11.3.1.5 Assessing the clinician response to recording of a HbA1c > 58 mmol/mol among individuals initiated on sitagliptin or sulphonylureas

In total, 2,695 (65.3%) individuals treated with sitagliptin and 12,476 (64.0%) individuals treated with sulphonylureas of my initial cohort, recorded an inadequate HbA1c > 58 mmol/mol during the 30 months of follow-up. However, only 1,739 (42.1%) individuals prescribed sitagliptin and 5,147 (26.4%) individuals prescribed sulphonylureas had a treatment regimen change recorded during this same period. This in itself, provided evidence of clinical inertia, which has been highlighted before as a major challenge in management of T2DM in "real world" clinical practice.[74,176] Clinical inertia is an issue that trials have been unable to account for when evaluating diabetes treatment effectiveness, as by their inherent design, they create an environment, and tend to recruit individuals, neither of which are truly reflective of actual clinical practice. Though the inertia for treatment change was evident with both add-on treatments, I found that the likelihood of treatment change was two-fold higher among individuals initiated on sitagliptin. Given that individuals prescribed sitagliptin were only 11% more likely to record a HbA1c > 58 mmol/mol, one would not expect these individuals to be 97% more likely to have their treatment changed compared to those prescribed sulphonylureas. Clinical inertia is undoubtedly

a complex phenomenon in T2DM and can be linked to several causes including physician, patient and healthcare-system related factors.[177] However there is evidence in this study of differential inertia patterns emerging between individuals prescribed different treatments: sitagliptin vs sulphonylureas. Treatment specific variation in clinical inertia has not been evaluated before.

There are several arguments as to why there may be a higher risk of treatment change among those prescribed sitagliptin. One such argument could be greater individual intolerance to sitagliptin due to a higher rate of adverse effects leading to greater rate of treatment change. However this is highly unlikely because extensive research from trials and observational studies has already shown sitagliptin to have a more favourable safety profile than sulphonylureas and better tolerability.[41,63,162] Hence, given both achieved glycaemic targets similarly, it is far more plausible that this higher risk of treatment change with sitagliptin is actually due to a greater inertia for treatment change among those prescribed sulphonylureas. This may be linked to the higher risk of hypoglycaemias with sulphonylureas compared to all other anti-diabetic treatments apart from insulin.[162] This means that sulphonylureas must firstly, be used with greater caution when further anti-diabetic therapy is added, and secondly, be gradually dose-titrated.

Firstly, clinician awareness that the risk of hypoglycaemia is increased when other treatments are added to sulphonylureas may result in a more cautious approach to further intensification (which is even greater among older adults aged ≥ 75). This hypothesis is supported by my subgroup analysis where I found no significant difference in risk of treatment change among those that switched treatment (i.e. stopped sulphonylureas or sitagliptin in place of another anti-diabetic treatment) [HR 1.08 (95%CI 0.99 to 1.18) in those aged 18-75 years] and [HR 1.04 (95%CI 0.76 to 1.43) in those aged ≥ 75 years]. However, a significantly higher rate of change with sitagliptin was observed among those that intensified only [HR 1.36 (95% CI 1.25 to 1.48) in those aged 18-75] and [HR 1.61 (95% CI 1.08 to 2.42) in those aged ≥ 75 years].

Secondly, unlike sitagliptin, sulphonylureas must be dose-titrated, starting at a low dose and as per guidelines, titrated at usually two-weekly intervals till the maximal tolerated dose is achieved.[178] Monitoring of the individuals response at two-weekly intervals requires an assessment of glycaemic response (often by pre-meal capillary blood glucose tests) and gathering a history to ensure no evidence of hypoglycaemias before the sulphonylureas can be up-titrated to the next step. For example, with gliclazide, the most commonly prescribed sulphonylureas in my study, treatment may be started on 80mg once daily, and then increased at two-weekly intervals to initially 80mg twice daily, then e.g.160mg morning and 80mg evening

before the final maximal dose of 160mg twice daily may be reached.[178] In an ideal scenario, this may take 6 weeks with 4 healthcare contacts to monitor dose titration. This titration requires an even more caution approach in older individuals and those subgroups more vulnerable to hypoglycaemic episodes.[178] In clinical practice this may mean, that several appointments are required before the optimal dose is reached. Therefore, if this is drawn out over a longer period (perhaps if regular clinical contacts are not arranged or possible), it could feasibly create inertia for treatment change. In contrast, sitagliptin will be commenced at the maximum dose suitable for that individual based on renal function and will not need titration thereafter.[27] Therefore, if at the next visit (ideally after 3 months), the HbA1c response to sitagliptin is not adequate, clinicians can change treatment immediately as dose titration is not an option. However in a similar timeframe with a sulphonylurea such as gliclazide, they may be in the process of titrating the regimen and thus consider it unsuitable to change treatment as the optimal dose may not yet have been reached. This hypothesis is supported by my analysis which showed that only 1,151 (9.3%) of individuals prescribed sulphonylureas had an anti-diabetic treatment change introduced within 3 months of recording a HbA1c > 58 mmol/mol compared to 616 (22.8%) of individuals prescribed sitagliptin. Of those who had no treatment change introduced and were prescribed sulphonylureas, 1,806 (17.3%) had their dose increased while only 10 (0.6%) of those prescribed sitagliptin had their dose increased.

Though a marked anti-diabetic treatment inertia is evident with both individuals prescribed sitagliptin and sulphonylureas, clinicians were more reluctant to add-on treatment to sulphonylureas and often preferred to increase dosage instead. This dose increase could however, arguably have been done sooner had the dose been titrated as recommended. The implications of these findings will be discussed further in Section 11.5 after outlining some of the methodological findings of this thesis.

11.3.2 Comparison of methodological approaches and findings for main cohort studies in Chapters 9 and 10 with existing literature

I employed several methodological concepts and approaches in my cohort studies to try to overcome some of the challenges commonly faced when undertaking observational studies of effectiveness. Establishing causality in any observational study is a major challenge, due to the risk of confounding bias. One advantage for this piece of work was that because several trials had been completed previously, I had sufficient evidence that a causal relationship does exist between prescribing of sitagliptin or sulphonylureas and changes in HbA1c and weight. In fact,

all criteria required for existence of causality as proposed by Bradford Hill can be considered fulfilled as shown in Table 11.1.[179,180]

Table 11.1 Bradford Hill Criteria for attributing causality to an exposure-outcome relationship as applied to this work

Bradford Hill Criteria	Explanation	As applied to my research question
Strength of association	a strong association is more likely to be causal than a modest one	An absolute reduction of 9.6 mmol/mol and 14.2 mmol/mol was observed in this study around 12 months, after initiation with sitagliptin and sulphonylureas respectively in this study and weight changes observed was also similar to previously completed trials
Consistency	relationship is repeatedly observed	My results for change in HbA1c and weight were similar to those observed in previous studies (Fig 11.1)
Specificity	the exposures specifically influence a particular outcome or population	Extensive theory and previous studies have explained how both treatments affect glycaemic control
Temporality	the exposures precede the outcome	Evident in study design
Biological gradient	the outcome is affected by the dose of exposure	This has been shown to be the case in trials as well
Plausibility	observed association can be plausibly explained by substantive matter	As above
Coherence	a causal conclusion should not contradict substantive knowledge	My findings support existing knowledge
Experiment	randomised experiments are best at determining causation	My study is observational however findings are in line with results from previous randomised trials
Analogy	for analogous exposures and outcomes an effect has already been shown	As above

The biggest challenge in my studies has been transitioning from demonstrating a causal relationship in a more controlled randomised experimental setting to demonstrating it accurately in an observational setting. This required several methodological considerations, to remove potential bias from my causal estimates as detailed below.

11.3.2.1 Challenges demonstrating causality in Observational Studies of effectiveness compared to Randomised Controlled Trials

In Chapter 4 (Section 4.2), I highlighted how randomised controlled trials are the gold standard to determine efficacy of a pharmacological intervention. Their main methodological advantage is that through prospectively randomising individuals in the study to either the intervention or comparator, both known and unknown confounding, information and selection bias can be

eliminated.[80] The limitation with RCTs (beyond their considerable expense) is that they often exclude older adults or those who are more comorbid which limits the generalizability of their findings. However, once a pharmacological treatment has been licensed, little incentive remains for license holders to further evaluate effectiveness in such populations by means of expensive RCTs. This is where nonexperimental observational effectiveness studies as undertaken in this thesis can be of value. However, non-random assignment of the interventions in such studies means that bias needs to be actively controlled for in the study design and analyses. The core component essential for observational effectiveness research is that the treatment groups being compared must have the same underlying risk for the outcomes of interest prior to implementing the interventions.[181] I detail below the approaches I used to achieve this in my studies.

11.3.2.1.1 Confounding Bias

Confounding by indication also known as "channelling bias" is the biggest challenge in observational studies of effectiveness. This exists when the likelihood of being allocated a particular treatment is based on particular characteristics of individuals and/or prognosis/severity of disease. For example, sitagliptin is more likely to be prescribed among individuals who are heavier (sulphonylureas known to cause weight gain) or in those with a history of hypoglycaemia (sulphonylureas known to cause hypoglycaemias) (detailed in Chapter 6, Section 6.4.1, Table 6.2).[181]

In order to control for risk of confounding within an observational study, I identified, confounders through exploring covariate-exposure (Chapter 6) and covariate-outcome (Chapter 7) relationships. This helped build the most parsimonious models for the main analysis. I also used Direct Acyclic Graphs (DAGs) to identify relevant confounders *a priori*, based on theoretical knowledge which I referred to as clinical models. Both analysis approaches ultimately yielded similar final estimates.[181]

Adjusting for confounding variables, of course, only accounts for imbalances due to confounders which have been measured and recorded in the dataset. Unmeasured confounding remains a significant challenge in observational studies. The DAG approach had the advantage of allowing me to identify potential confounders that were not well measured (or measured at all) in the dataset. This included, for example information on diet and exercise levels which are not recorded in the THIN database, since they are difficult to capture in routinely collected healthcare data. In such instances, where possible, I used proxy-variables such as Townsend quintiles (a measure

of social deprivation) and weight, as proxies to help explain some of the variation in diet and exercise. This of course is not ideal and remains a study limitation.

11.3.2.1.2 Information Bias

Information Bias refers to a distortion in treatment effect estimates due to measurement error or misclassification in variables used in the study e.g. exposures, confounders or outcomes. This type of error may be non-differential or differential, each of which poses different problems.[182] Non-differential misclassification or measurement error means that the frequency of errors is approximately the same in each group being compared. This type of error in exposure or outcome will bias the results of the study towards the null, while in confounders it will lead to residual confounding.[182] Differential errors where errors occur with greater frequency in one of the study groups can also lead to bias.[181]

Information bias relating to my exposure measurement (prescribing of sitagliptin or sulphonylureas) was minimised, as the prescription data in THIN are automatically generated, when a clinician decides to commence an individual on a particular therapy. Equally, the outcomes of HbA1c and weight are objective and recorded routinely in individual records. I also showed in Chapter 7 (Section 7.4.2.1) that patterns of recording for HbA1c and weight for both individuals prescribed sitagliptin and sulphonylureas were similar. I have tried to minimise information bias relating to history of comorbidities and concomitant prescribing by carefully developing codelists to capture the history of these diseases and having these reviewed by another senior clinician. I have used anonymised free text information where I believed codelists alone may not have been sufficient to capture the history of a comorbidity e.g. for hypoglycaemias. Prescribing of a treatment however does not equate to adherence to treatment. In order to account for the lack of information regarding adherence, I undertook additional subgroup analysis. Here, I analysed the subgroup of individuals who had been prescribed sitagliptin and sulphonylureas continuously for the study period with no greater than a 60 day gap between successive prescriptions. The results of this analysis were then compared with the overall main analysis which included all individuals with at least one prescription for either treatment of interest. These subgroup analyses supported the findings from the main analysis and helped make overall conclusions more robust.

11.3.2.1.3 Selection Bias

This type of bias can occur in observational studies if subjects are erroneously chosen in a manner that generates a cohort of individuals who are not fully representative of all treatment

users.[181,182] For example, those with complete data reported at baseline and study end may be inherently different to those with missing data.

I adopted three approaches to help ensure the risk of this bias was minimal. Firstly, I undertook an in-depth comparison of characteristics of individuals initiated on sitagliptin vs sulphonylureas, and adjusted for relevant confounding variables identified in each analysis. Secondly I examined the frequency for recording of HbA1c and weight among both treatment groups over time. Thirdly, I compared the characteristics of sitagliptin and sulphonylurea initiators for those with and without missing data. These latter two steps confirmed there were no significant disparities that could bias analysis.

11.3.2.2 Further methodological approaches employed for controlling bias in the studies

I employed several additional methodological approaches to further help control for potential bias in my cohort studies.

11.3.2.2.1 <u>New-user design</u>

New-user designs follow individuals from when they are first prescribed a given treatment excluding persistent-users who may have been on the treatments previously. This design overcomes problems associated with inclusion of individuals who are persistent with a treatment because it allows for adjustment for confounders at baseline when treatment initiation decision was made and eliminates selection bias during follow-up.[181] In the cohort studies presented in Chapters 9 and 10, I only included new users of sitagliptin and sulphonylureas, by ensuring that they have received no prescription for any other anti-diabetic drug other than metformin prior to the index date of first prescription.

11.3.2.2.2 <u>Choice of comparator and clinical equipoise</u>

Comparative effectiveness research is most robust when different treatment options are being compared as opposed to when treated and untreated groups are compared.[79] I compared two treatments for the same indication at the same point in the clinical pathway (2nd line usage after metformin for T2DM), which helped considerably reduce the potential for bias due to confounding. As evidenced from national and international guidance from NICE, European Association for study of Diabetes (EASD) and American Diabetes Association (ADA), there is limited prognostic data to clinically guide prescriber choice between commencements of either of these two agents.[22,24] Clinicians may consider some prognostic factors at the point of prescribing including that sulphonylureas may increase weight and risk of hypoglycaemia. However, I could capture recording of these factors at baseline and hence control for these confounders in the analysis.

Through controlling for these confounders, a situation of clinical equipoise was created - such a situation was ideal to control for confounding.[181]

Additionally, by ensuring that sitagliptin and sulphonylurea users were compared across a similar time period, any bias due to time-related influences was also minimised.

11.3.2.2.3 Multivariable models and use of propensity scores

The main approach I undertook for the analyses in Chapters 9 and 10 involved use of traditional multivariable regression analysis. I also undertook propensity score matching analysis in the cohort studies exploring change in HbA1c and weight after baseline which served as supportive analyses. The propensity score was used to match individuals who fell within similar strata of the propensity score and hence were similar in terms of observed variables.[79,126,171] I was able to successfully match both individuals prescribed sitagliptin and sulphonylureas within a 0.05 caliper size and remove any significant difference in confounder characteristics distribution at baseline between the groups. The estimate yielded from propensity score matching and regression analysis after full adjustment were highly similar: for change in HbA1c from baseline: [Average Treatment Effect after Propensity Score Matching 0.83 mmol/mol (95% CI 0.04 to 1.60) vs estimate from multivariable regression analysis 0.89 mmol/mol (95% CI 0.33 to 1.45)] while for change in weight from baseline [Average Treatment effect after Propensity Score Matching -2.30 kg (95% CI -3.05 to -1.56) vs estimate from multivariable regression analysis -2.26 (95% CI -2.48 to -2.04)]. Propensity score matching has proved useful in several studies from a conceptual point of view, as it allows one to assess the success of matching for removing baseline differences in measured covariates. Matching does however, lead to smaller sample size as those who cannot be matched must be removed from analysis unless matching criteria are made less restrictive.[170] Evidence of this can be seen in estimates above, which are less precise with wider confidence intervals for the propensity score matching analyses. And of course, as with multivariable regression modelling, propensity score matching cannot remove bias that may arise due to unmeasured confounding.[171]

11.3.2.3 Challenge of Missing Data

Several potential confounding variables were found to have missing data at baseline, presented in details in Chapters 9 and 10. Covariates with missing data at baseline included weight, HbA1c, Townsend quintiles and smoking status. In both chapters, I showed that patterns of missingness were similar between both sitagliptin and sulphonylurea groups and there was no strong evidence

to suggest that individuals with missing data differed systematically from those with complete data.

11.4 Strengths and Limitations

The cohort studies presented in Chapters 9 and 10 in this thesis have several notable strengths. Firstly, my studies are the largest of their kind undertaken using data from actual clinical practice, and thus provide insight into “real world” effectiveness of sitagliptin compared to sulphonylureas as add-on to metformin. The individuals included in my studies spanned all adult ages, with over 2,000 individuals included who were aged ≥ 75 years. I placed no restriction in terms of comorbidities for exclusion from this study which meant the results are more reflective of individuals routinely seen in actual clinical practice, who are often comorbid. This was important, because the majority of previous trials and observational studies have excluded such older and comorbid individuals despite the fact that these individuals more often require diabetes treatment. Secondly, I analysed the data in 2 ways: firstly using a traditional regression analysis using confounders demonstrated to have statistical association with exposure and outcome; and then using *a priori* agreed confounders in all cohort studies. For the analysis on change in HbA1c and weight, I used a third approach involving propensity score matching analysis. The purpose of using multiple approaches was to help ensure findings remained consistent across methods which was indeed the case. Thirdly, several methodological concepts such as the use of a new user design described earlier and use of an active comparator helped provide further methodological strength to this work.

There are several clinical and methodological limitations to acknowledge as well. Firstly, I have focused my thesis entirely on comparative effectiveness work examining sitagliptin and not the gliptin class of medications as a whole. This is because sitagliptin is the most widely prescribed gliptin in the US and UK accounting for over 70% of all gliptins prescribed (Chapter 5, Section 5.4.3.3, Figure 5.3). Hence, epidemiological data in primary care databases like THIN relating to the other gliptins is very limited. This was not an issue in the case of sulphonylureas, hence these were grouped together. Secondly, cost effectiveness is of course, also an important consideration when prescribing decisions are made. This however, has not been examined in this piece of work where the focus has been entirely on clinical effectiveness. Thirdly, sitagliptin and sulphonylureas are only two possible add-on treatments that can be used after metformin for T2DM – thiazolidinediones, insulin, GLP-1 analogues and more recently SGLT-2 inhibitors are other

possible alternatives. However, once again their use was much less widespread at time of commencement of this thesis as evidenced in Chapter 5 (Section 5.4.3.3, Figure 5.3). Hence, I have focussed on the most common decision faced in clinical practice: sitagliptin vs sulphonylureas as add-on to metformin.

There are also methodological limitations to consider. Firstly, only 71.5% of the initial cohort could be included in the analysis on change in HbA1c from baseline and 67.1% of the initial cohort could be included in the analysis on weight. This is largely due to the fact that only these respective percentages had the outcome recorded between the desired 9-18 month interval after baseline. This is because recording of HbA1c and weight in clinical practice is simply not as frequent as the 3-6 monthly intervals recommended in guidelines and conformed to in previous prospective observational studies and trials. Secondly, nearly 4% of individuals included in the cohort studies examining time to first recording of a HbA1c > 58 mmol/mol and first treatment change had to be excluded due to lack of a HbA1c recording after the index date. Analysis of an extensive set of demographic and clinical characteristics across those with missing data and those without, however did not suggest any systematic differences.

As with any observational study, controlling for confounding is a major challenge to ensuring estimates obtained are reliable. Despite extensive analytical and epidemiological measures employed, one can never be fully sure that all confounding has been removed as unmeasured confounders may still influence findings. The fact that the estimates for change in HbA1c and weight for those aged 18-75 years align so closely with previously completed trials helps give credibility to my results and provides some evidence that I may have successfully controlled for confounding. Moreover, this meant that when I extended my analysis to examine those aged ≥ 75 years as well as outcomes examining time to recording of first HbA1c > 58 mmol/mol and treatment change which had not been studied before, there was greater confidence (as I had already demonstrated I could control for confounding).

Finally, as prescribing of a treatment could not guarantee adherence, I undertook two separate pieces of analysis to try overcome this limitation: the main analysis examining all those who had at least one prescription for the add-on treatment (akin to an “intention to treat” analysis within a Randomised Controlled Trial) and then a secondary subgroup analysis examining only those individuals issued successive prescriptions for metformin and the add-on treatment for the entire study duration (akin to a “per-protocol” analysis within a Randomised Controlled Trial). Across all

four cohort studies, findings from this subgroup analysis were consistent with that observed with the full cohort.

11.5 Implications of findings for Clinical Practice and Public Health

The algorithm that I generated to help identify individuals with type 1 and type 2 diabetes mellitus in a large primary care database has wider potential applications beyond this thesis. It can be used, in particular, for future epidemiological and public health work related to diabetes. Furthermore, with some minor modifications, it can be adapted easily for use in other countries. ICD-10 (International Classification of Diseases) codes or other hierarchical coding systems indicative of DM could be used instead of Read Codes while pharmacological therapy and other thresholds used e.g. for age at diagnosis could be modified as necessary according to local treatment and monitoring guidelines.

The study examining trends in incidence, prevalence and prescribing for T2DM in Chapter 5 reemphasised the rising incidence and prevalence of T2DM in the UK, which is of significant concern to public health. The significant strain on National Health Service (NHS) resources in the UK which is already apparent is likely to worsen if these current trends continue. In this study, several subgroups were also identified as being at higher risk of developing T2DM such as men, older individuals and those from more deprived areas. These are clearly groups that should be targeted more closely for preventative health intervention going forward. The study also provided evidence that prescribing patterns in UK primary care closely reflected clinical guidance from NICE in particular. Metformin emerged as the most widely prescribed agent though sulphonylureas, remained the second most common therapy prescribed.

The main collective goal of the four cohort studies undertaken in this thesis was to investigate “real world” comparative effectiveness of sitagliptin compared to sulphonylureas as add-on to metformin. This could inform clinician prescribing decisions when choosing between both treatments based on effectiveness (once safety had been considered). This was needed as national guidelines from National Institute for Health and Care Excellence (NICE), but also from other major international bodies such as the European Association for Study of Diabetes (EASD), the American Diabetes Association (ADA) and International Diabetes Federation do not discriminate between the two treatments based on effectiveness.[22,24,39]

My cohort study examining change in HbA1c from baseline helped to externally validate results seen in trials that the glycaemic change observed with sitagliptin and sulphonylureas when added

to metformin is indeed similar. I was able to demonstrate that this held true for older individuals aged ≥ 75 years and also comorbid individuals often previously excluded from trials. Some clinical studies previously suggested that sulphonylureas produce a greater glycaemic reduction than sitagliptin,[58,62] however after adjustment for confounders in my study this was found not to be the case. This false impression may be linked to a more rapid glycaemic reduction seen at 6 months with sulphonylureas which gradually levels off thereafter. I demonstrated that a comparative weight reduction of approximately 2.3kg was observed with sitagliptin compared to sulphonylureas at 12 months which was linked to a 1.4kg increase observed among sulphonylurea initiators and 1.4kg decrease observed with sitagliptin. Sitagliptin is generally accepted to be weight neutral, however some statistically significant weight loss is evident. Even though 2.3kg may not be of great magnitude, external validation of this finding within a cohort of individuals seen in routine clinical practice was important. This is because a reduction of this amount has been shown to improve physical and emotional health,[72] and weight loss has been repeatedly shown to correlate closely with improved T2DM control.[136,183] Interestingly, the comparative weight loss observed was lower in older individuals aged ≥ 75 years, at approximately 1.3 kg. This was because weight gain with sulphonylureas was not observed to occur in this older population though weight loss with sitagliptin was still evident. Thus, if treatment is being prescribed in older individuals aged ≥ 75 years who are overweight, further weight gain with sulphonylureas may not be of concern while some beneficial weight loss may be obtained with sitagliptin.

Thus in total, an equivalent glycaemic but superior weight change was observed in my "real world" studies with sitagliptin. Therefore, from a clinical effectiveness point of view, the results would support the position statement of the American Association of Clinical Endocrinologists (AACE/ACE) rather than NICE and the major bodies mentioned earlier.[38] This is because AACE/ACE are the only body that recommend sitagliptin (and indeed other gliptin usage) as add-on ahead of sulphonylureas for second-line treatment.[38]

My cohort studies examining time to first recording of a HbA1c > 58 mmol/mol and anti-diabetic treatment change revealed that despite similar effectiveness in achieving glycaemic targets, a clinical inertia for treatment change was evident after initiating both treatments. Among those that had a recorded HbA1c > 58 mmol/mol, 66.4%(n=1,789) of those prescribed sitagliptin and 83.7% (n=10,446) of those prescribed sulphonylureas as add-on to metformin had no treatment change within 3 months of recording this HbA1c despite NICE recommendations advocating this.[22]

Treatment inertia has been well documented as a major challenge in management of T2DM,[74,176] and I have demonstrated that this inertia for treatment change appears greater with sulphonylureas. Though only an 11% higher rate of recording of HbA1c > 58 mmol/mol was evident with those prescribed sitagliptin vs sulphonylureas, the rate of treatment change was almost double with sitagliptin users. This greater inertia evident with sulphonylureas can be partly explained by the fact that in 1,806 (17.3%) of these 10,446 individuals that recorded a HbA1c > 58 mmol/mol and no treatment change; the dose of sulphonylureas had been increased when in contrast, this happened only in 10 (0.6%) of 1,789 sitagliptin users. Still, it is not desirable for clinicians in the majority of cases, to wait for further HbA1c recordings to optimise sulphonylurea dosing which can be done using blood glucose monitoring with support from clinicians at home. This unnecessary time delay keeps individuals in sub-optimal glycaemic control for longer than is necessary, increasing the risk of longer-term T2DM complications. Individuals enrolled in trials are usually more empowered to control their own illness and are monitored more closely. Hence, this particular form of inertia that I have highlighted is not readily identifiable in the trial setting. Studies examining inertia often focus on individual and physician factors causing inertia, however choice of treatment may also play a role here as I have identified.[176]

Tackling clinical inertia in management of T2DM has been a major clinical and public health challenge. Guidelines from NICE and other international bodies all advocate aggressive treatment change if glycaemic control is suboptimal. However, as further evidenced from my studies, inertia is highly prevalent with both of these two widely used add-on medications in clinical practice. My findings highlight that further support and training needs to be given to clinicians to give them the confidence and resources needed to change treatment quicker and with sulphonylureas, to titrate doses more rapidly rather than waiting for further HbA1c measurements (unless home blood glucose monitoring is not possible, which is rare).

11.6 Implications for Future Research

As evidenced from my cohort studies, there is a need to confirm and eliminate the barriers preventing clinicians changing anti-diabetic treatment regimens when add-on therapy with sitagliptin or sulphonylureas has failed to maintain glycaemic control. This is because NHS expenditure on diabetes is known to be rising considerably and sub-optimal glycaemic control which leads to longer-term complications of T2DM is a major contributory factor.[8]

My systematic review (Chapter 2) highlighted several important gaps in the literature relating to comparative effectiveness work with sitagliptin and sulphonylureas as add-on to metformin. It was not possible to examine all of these gaps within this thesis, and I have focused on exploring the short to medium term effectiveness outcomes. This is because, prior to examining longer-term outcomes, I needed to demonstrate a methodological ability to examine short to medium term outcomes using a primary care database and overcome the confounding challenges commonly faced in observational studies of effectiveness, detailed earlier. Secondly, for the longer-term outcomes, I was able to realise that the sample size available for sitagliptin was insufficient, and that I would need more longitudinal data to accumulate given sitagliptin was licensed in the UK only in 2007.

Longer-term gaps in comparative effectiveness literature identified for sitagliptin compared to sulphonylureas related largely to microvascular and macrovascular complications of T2DM such as the occurrence of cardiovascular events, retinopathy, neuropathy and nephropathy. The absence of these complications is indicative of better longer-term management of diabetes while their presence is strongly associated with reduced quality of life.[64] A cardiovascular outcome study comparing sitagliptin to placebo has been conducted recently,[44] and showed no increased cardiovascular risk, however a direct comparative effectiveness study between a gliptin and sulphonylureas will not emerge till 2019 with the results from the CAROLINA study.[184] Equally, the effect of sulphonylureas on cardiovascular disease is still poorly understood despite many years of usage. [66,185] A comparative effectiveness pragmatic clinical trial, The Glycemia Reduction Approaches in Diabetes (GRADE) study is also underway which will compare sitagliptin to sulphonylureas in individuals with T2DM inadequately controlled on metformin for longer-term complications.[186] However, the results of this trial are not expected to be available before 2020. Cohort studies could help evaluate comparative effectiveness here, however large datasets with long follow-up time will be needed to evaluate these macrovascular and microvascular outcomes. Addressing some of these longer-term gaps in evidence will form the basis of post-doctoral work.

11.7 Conclusions

This thesis has provided a novel algorithm for identification of individuals with type 1 and type 2 diabetes mellitus for use in primary care databases, both in the UK and with some modification, for use worldwide. I have also proved a detailed overview of incidence, prevalence and prescribing for type 2 diabetes mellitus in the UK between 2000 and 2013 and undertaken a

comprehensive systematic review examining literature focused on comparative effectiveness of sitagliptin to sulphonylureas as add-on to metformin. These initial studies laid the foundation for the main focus of this thesis – evaluating effectiveness of sitagliptin compared to sulphonylureas as add-on to metformin in “real world” clinical practice. Specifically, the clinical evidence from this thesis helped validate previous clinical trial findings in a more diverse and comorbid population. I demonstrated no significant difference in HbA1c change between both treatments after approximately 12 months, however comparative weight loss of close to 2.3 kg with sitagliptin. I also demonstrated an equivalent effectiveness in older individuals aged ≥ 75 years for sitagliptin compared to sulphonylureas. I found that individuals prescribed sitagliptin were equally likely to maintain glycaemic targets as sulphonylurea initiators, however nearly twice as likely to record an anti-diabetic treatment change. This analysis also revealed an inertia for changing treatment once suboptimal glycaemic control had been identified, to be prevalent in both add-on groups. This inertia was however, greater among those prescribed sulphonylureas and in older adults aged ≥ 75 years. These findings indicated further research is needed to confirm and eliminate the barriers that exist to clinicians changing treatment in a timelier manner after sitagliptin or sulphonylureas add-on has proved inadequate. Further work evaluating longer-term comparative effectiveness of both add-on treatments is also needed.

From a methodological perspective, this work provided a systematic approach to undertaking observational studies of effectiveness, which may be of use for future researchers undertaking epidemiological research into type 2 diabetes mellitus or indeed other disciplines.

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Appendix A. **Supplementary Material for Chapter 2**

Supplementary Methods 2A1. Systematic Review Protocol as published on PROSPERO

Review question(s)

To review the **effectiveness** of the dipeptidyl peptidase-4 inhibitor, sitagliptin compared to sulphonylureas for glycaemic control, weight control and for complications of type 2 diabetes mellitus in adult patients on metformin therapy using phase 3 randomised controlled trials and observational studies.

Search Strategy

Electronic searches will be conducted for randomised controlled trials, observational studies and conference abstracts using MEDLINE, EMBASE, the Cochrane Central Register of Control Trials (CENTRAL). Search strategies will be developed for individual databases and reviewed by an information specialist in the area to ensure rigour. Additional studies and grey literature will be retrieved by screening references of retrieved studies and by searching International Pharmacy Abstracts, conference proceedings on Scopus and the WHO international clinical trial registry.

Types of study to be included

Randomised controlled trials and Observational Studies

Condition or domain being studied

Type 2 Diabetes Mellitus

Participants/ population

Patients inadequately controlled on metformin that require additional add-on therapy.

Intervention(s), exposure(s)

Sitagliptin (Dipeptidyl-peptidase-4 inhibitor)

Comparator(s)/ control

Any drug belonging to the sulphonylurea class (gliclazide, glipizide, gilbenclamide, tolbutamide, chlorpropamide, glimepiride)

Outcome(s)

Primary outcomes

Primary Outcomes of Interest in both RCT and Observational Studies will examine difference between groups for:

1. Change in HbA1C from baseline (mmol/mol)

Secondary outcomes (where reported)

1. Number achieving HbA1C at study end <7.0% (<53mmol/mol)
2. Number achieving HbA1C at study end<6.5% (48mmol/mol)
3. Change in Fasting plasma glucose from baseline
4. Change in weight from baseline (kg)
5. Change in BMI from baseline (kg/m2)
6. Change in blood pressure from baseline (mmHg)
7. Change in cholesterol from baseline (mmol/mol)
8. Other effectiveness outcomes relating to reduction in onset of complications of diabetes e.g. nephropathy, neuropathy, retinopathy, onset of cardiovascular disease, occurrence of cardiovascular events e.g. myocardial infarction, stroke, hospitalisation due to angina or heart failure.
9. Any longer-term effectiveness outcomes i.e. follow-up of greater than 104 weeks

Data extraction, (selection and coding)

Microsoft Excel will be used to develop a data extraction spreadsheet. This will be piloted on a small selection of studies and adjusted accordingly. All data will be extracted by two reviewers independently and compared. Differences will be resolved through consensus or third and fourth reviewer consultation where necessary. Data will be gathered on study design and location, participant demographics, sitagliptin details (dose, frequency), sulphonylurea details (drug, dose, frequency), study withdrawal numbers and outcome data as specified. Data will be collected in as far as is possible using an intention to treat (ITT) approach.

Risk of bias (quality) assessment

The Cochrane Collaborations Risk of Bias Tool will be used to assess heterogeneity and quality in randomised controlled studies. All six criteria in the risk of bias tool will be graded as a) Low bias (green) b) Unclear bias (orange) or c) High bias (red).

The methodological quality of observational studies included will be assessed in line with the recommendations from the Cochrane Handbook for Systematic Reviews of Interventions on assessing the quality of non-randomised studies (Cochrane Handbook - Chapter 13).We will use the Newcastle-Ottawa quality assessment scales to assess the quality of cohort and case-control studies (Wells 2008) and present our assessment in a table. All study assessments will be carried out by two reviewers independently and checked for agreement. Differences will be resolved through consensus or in consultation with a third and fourth reviewer.

Strategy for data synthesis

We will follow the PRISMA guidelines for a systematic review. A flow diagram will illustrate the literature search and article selection process, and a table will provide an overview of

the characteristics of included articles. Standardised mean differences will be calculated for our continuous outcomes and odds ratios/relative risks for our dichotomous outcomes where possible.

If the included articles are of a sufficiently comparable quality and homogenous in outcomes, a meta-analysis for respective outcomes will be undertaken using Stata statistical software package (Version 13®). Heterogeneity in that instance will be assessed using the I-squared statistic, with an I-squared value greater than 75% considered indicative of significant heterogeneity. The extent of study heterogeneity will determine whether a fixed-effects or random-effects model is used in the analysis. Risk of publication bias will be assessed through a funnel plot. In instances where a high degree of bias is detected in a study as determined by risk of bias assessment, sensitivity analysis will be considered to determine impact of studies with high levels of bias on the analysis. The meta-analysis will be conducted in accordance with the PRISMA guidelines.

Given the wide range of research methods that are anticipated to occur in identified studies, statistical meta-analysis however may not be appropriate. In this instance, a descriptive analysis will be used and a comprehensive account of study quality, strengths and limitations will be reported in a tabulated summary. Forest plots will be created to allow for direct visual comparisons to be made between the studies. Study recommendation and potential avenues for future research will likewise be reported.

Analysis of subgroups or subsets

We will conduct several subgroup analysis in addition to above including an analysis of results of randomised controlled trials and observational studies separately. We will also conduct sensitivity analysis by study duration and study quality.

Dissemination plans

We will disseminate the research results through peer reviewed journals and conference presentations.

Supplementary Methods 2A2. Search Strategy in EMBASE.
Database: Embase <1980 to 2015 Week 43>
Search Strategy:
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1 exp metformin/ (39879)
2 metformin.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (41520)
3 glucophage.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1473)
4 dimethylbiguanidine.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (3)
5 dimethylguanylguanidine.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2)
6 1 or 2 or 3 or 4 or 5 (41532)
7 exp sitagliptin/ (5031)
8 sitagliptin.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (5216)
9 Januvia.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (698)
10 ("Mk 0431" or mk 431 or mk0431 or mk431 or ono 5435 or ono5435).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (193)
11 ristaben.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (8)
12 sitagliptine.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (48)
13 tesavel.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (12)
14 xelevia.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (32)
15 Glactiv.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (7)
16 or/7-15 (5228)
17 6 and 16 (3046)
18 exp sulfonylurea/ (10374)
19 sulphonylurea*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2940)
20 sulphonylureas.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1328)
21 sulfonylurea*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (22171)
22 sulfonylurea.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (20994)
23 (sulfonurea or sulfonyl urea or sulfonylcarbamide or sulphonurea).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (168)
24 or/18-23 (23245)
25 17 and 24 (1651)
26 Clinical study/ (70420)
27 Case control study.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (133957)
28 Family study/ (10937)
29 Longitudinal study/ (82511)
30 Retrospective study/ (432735)
31 Prospective study/ (311493)
32 Randomized controlled trials/ (85652)
33 31 not 32 (309109)
34 Cohort analysis/ (220411)
35 (Cohort adj (study or studies)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (150359)
36 (Case control adj (study or studies)).tw. (88705)
37 (follow up adj (study or studies)).tw. (47930)

38 (observational adj (study or studies)).tw. (82562)
39 (epidemiologic$ adj (study or studies)).tw. (80707)
40 (cross sectional adj (study or studies)).tw. (109506)
41 or/26-30,33-40 (1421985)
42 Clinical trial/ (852134)
43 Randomized controlled trial/ (386850)
44 Randomization/ (68432)
45 Single blind procedure/ (21172)
46 Double blind procedure/ (124394)
47 Crossover procedure/ (44827)
48 Placebo/ (264947)
49 Randomi?ed controlled trial$.tw. (125572)
50 Rct.tw. (18572)
51 Random allocation.tw. (1460)
52 Randomly allocated.tw. (23491)
53 Allocated randomly.tw. (2066)
54 (allocated adj2 random).tw. (739)
55 Single blind$.tw. (16493)
56 Double blind$.tw. (155737)
57 ((treble or triple) adj blind$).tw. (496)
58 Placebo$.tw. (222385)
59 Prospective study/ (311493)
60 or/42-59 (1514373)
61 Case study/ (34294)
62 Case report.tw. (292773)
63 Abstract report/ or letter/ (941827)
64 or/61-63 (1262329)
65 60 not 64 (1474343)
66 41 or 65 (2525050)
67 25 and 66 (992)

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Supplementary Methods 2A3. Search Strategy in MEDLINE.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

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1 exp Metformin/ (8560)
2 metformin.mp. (13210)
3 glucophage.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (94)
4 dimethylbiguanidine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1)
5 dimethylguanylguanidine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2)
6 1 or 2 or 3 or 4 or 5 (13226)
7 sitagliptin.mp. (1351)
8 Januvia.mp. (43)
9 ("Mk 0431" or mk 431 or mk0431 or mk431 or ono 5435 or ono5435).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (25)
10 ristaben.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (0)
11 sitagliptine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (22)
12 tesavel.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2)
13 xelevia.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (1)
14 Glactiv.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2)
15 or/7-14 (1363)
16 6 and 15 (436)
17 exp Sulfonylurea Compounds/ (16939)
18 sulphonylurea*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (2125)
19 sulphonylureas.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (981)
20 sulfonylurea*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (9629)
21 (sulfonurea or sulfonyl urea or sulfonylcarbamide or sulphonurea).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (114)
22 or/17-21 (21242)
23 16 and 22 (150)

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Supplementary Methods 2A4. Search Strategy in CENTRAL.

ID	Search
#1	"Metformin"
#2	"glucophage"
#3	"dimethylbiguanidine"
#4	"dimethylguanylguanidine"
#5	#1 or #2 or #3 or #4
#6	"sitagliptin"
#7	"Januvia"
#8	("Mk 0431" or mk 431 or mk0431 or mk431 or ono 5435 or ono5435)
#9	"ristaben"
#10	"sitagliptine"
#11	"tesavel"
#12	"xelevia"
#13	"Glactiv"
#14	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15	#5 and #14
#16	"sulphonylurea"
#17	"sulphonylurea$"
#18	"sulfonylurea"
#19	"sulfonylurea*"
#20	(sulfonurea or sulfonyl urea or sulfonylcarbamide or sulphonurea)
#21	#16 or #17 or #18 or #19 or #20
#22	#15 and #21 in Trials

Supplementary Methods 2A5. Newcastle Ottawa Scale

Note: A study can be awarded a maximum of one star ( ) for each numbered item within the Selection and Outcome categories. A
maximum of two stars can be given for Comparability.

Selection
1) Representativeness of the exposed cohort
a) truly representative of the average ⋯⋯⋯⋯⋯⋯ (describe) in the community
b) somewhat representative of the average ⋯⋯⋯⋯⋯⋯ in the community
c) selected group of users eg nurses, volunteers
d) no description of the derivation of the cohort

2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort
b) drawn from a different source
c) no description of the derivation of the non exposed cohort

3) Ascertainment of exposure
a) secure record (eg surgical records)
b) structured interview
c) written self report
d) no description

4) Demonstration that outcome of interest was not present at start of study
a) yes
b) no

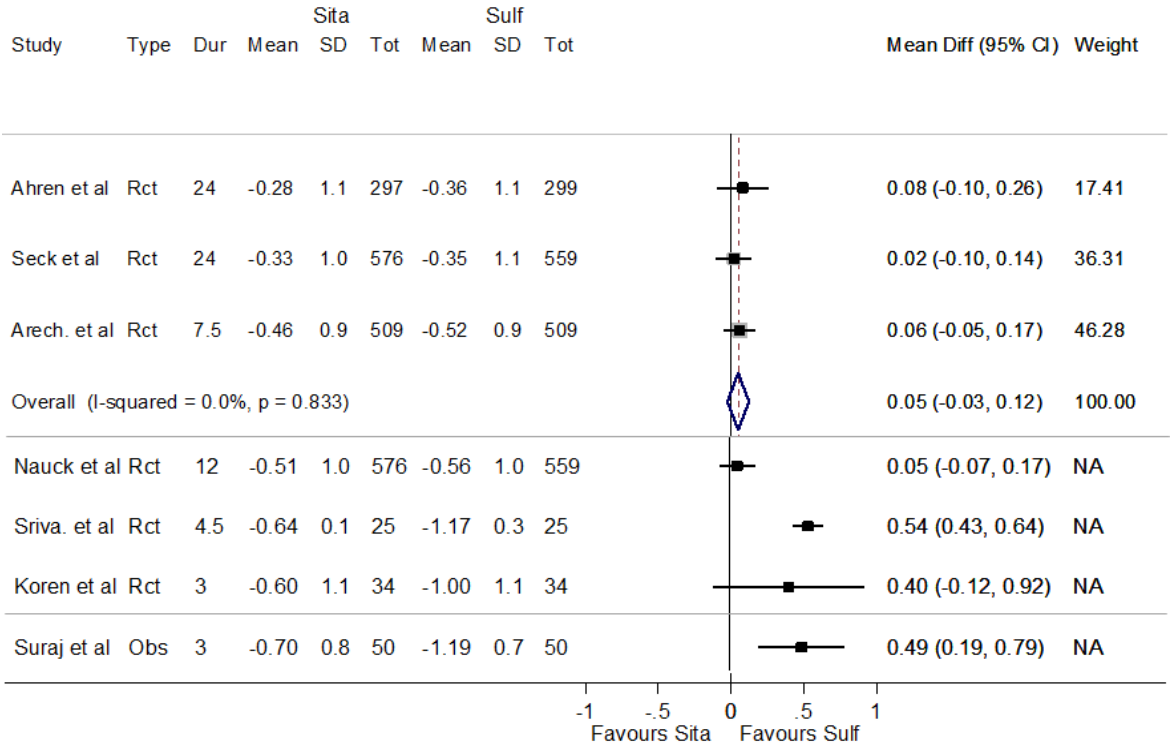
Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for ⋯⋯⋯⋯⋯⋯ (select the most important factor)
b) study controls for any additional factor (This criteria could be modified to indicate specific control for a second important
factor.)

Outcome
1) Assessment of outcome
a) independent blind assessment
b) record linkage
c) self report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow up period for outcome of interest)
b) no
3) Adequacy of follow up of cohorts
a) complete follow up - all subjects accounted for
b) subjects lost to follow up unlikely to introduce bias - small number lost - > ⋯⋯ % (select an adequate %) follow up, or description
provided of those lost)
c) follow up rate < ⋯⋯% (select an adequate %) and no description of those lost
d) no statement

Supplementary Table 2A1 Rationale for exclusion of studies from systematic review following review of full publications.

Studies Excluded	Rationale for Exclusion
1. The incidence of hypoglycaemia in Muslim patients with type 2 diabetes treated with sitagliptin or a sulphonylurea during Ramadan: a randomised trial[1]	Unsuitable comparator - Patients were not required to be on metformin
2. Sitagliptin Use in Patients With Diabetes and Heart Failure[2]	Unsuitable comparator - Patients were not required to be on metformin and sulphonylurea not used.
3. Safety and effectiveness of non-insulin glucose-lowering agents in the treatment of people with type 2 diabetes who observe Ramadan: a systematic review and meta-analysis[3]	Review/Meta-analysis only
4. Roadmap for oral antidiabetic therapy when sulfonylurea-metformin combination failed[4]	Unsuitable comparator – No sulphonylurea comparator group
5. Combination Therapy with a Dipeptidyl Peptidase-4 Inhibitor, Sulfonylurea, and Metformin Markedly Improves HbA1c Levels in Japanese Patients with Type 2 Diabetes Mellitus[5]	Unsuitable comparator - Case series with 3 patients and unsuitable comparators.
6. Comparative Study of Three DPP-4 Inhibitors, Namely Sitagliptin, Vildagliptin, and Alogliptin, in Japanese Type 2 Diabetic Patients: The COSVA Randomized, Controlled Trial[6]	Unsuitable comparator - No sulphonylurea comparator group
7. Real world clinical effectiveness of sitagliptin therapy for management of type 2 diabetes: a retrospective database analysis[7]	Unsuitable comparator - No sulphonylurea comparator group
8. The tolerability and safety of DPP-4 inhibitors for the treatment of older people with type 2 diabetes mellitus: an observational study[8]	Unsuitable comparator - No sulphonylurea comparator group
9. A single centre retrospective 12 months follow up study of safety and efficacy of sitagliptin[9]	Unsuitable comparator - Conference abstract where multiple unclear comparison groups
10. Retrospective Analysis on the Efficacy, Safety and Treatment Failure Group of Sitagliptin for Mean 10-Month Duration[10]	Unsuitable comparator - No sulphonylurea comparator group
11. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes[11]	Unsuitable comparator - No sulphonylurea comparator group
12. Comparative safety and effectiveness of sitagliptin in patients with type 2 diabetes: retrospective population based cohort study[12]	Unsuitable comparator - No sulphonylurea comparator group
13. Sitagliptin After Ischemic Stroke in Type 2 Diabetic Patients: A Nationwide Cohort Study[13]	Unsuitable comparator - No sulphonylurea comparator group
14. Hypoglycaemia in patients with type 2 diabetes from India and Malaysia treated with sitagliptin or a sulfonylurea during Ramadan: a randomized, pragmatic study[14]	Unsuitable comparator - No sulphonylurea comparator group
15. Cardiovascular Outcomes of Sitagliptin in Type 2 Diabetic Patients with Acute Myocardial Infarction, a Population-Based Cohort Study in Taiwan[15]	Unsuitable comparator - Comparator group could be on a multitude of different medicines not just sulphonylureas
16. Lower risk of hypoglycaemia with sitagliptin compared to glipizide when either is added to metformin therapy: a	Safety only – No efficacy/effectiveness outcome reported. Only hypoglycaemia incidence reported.

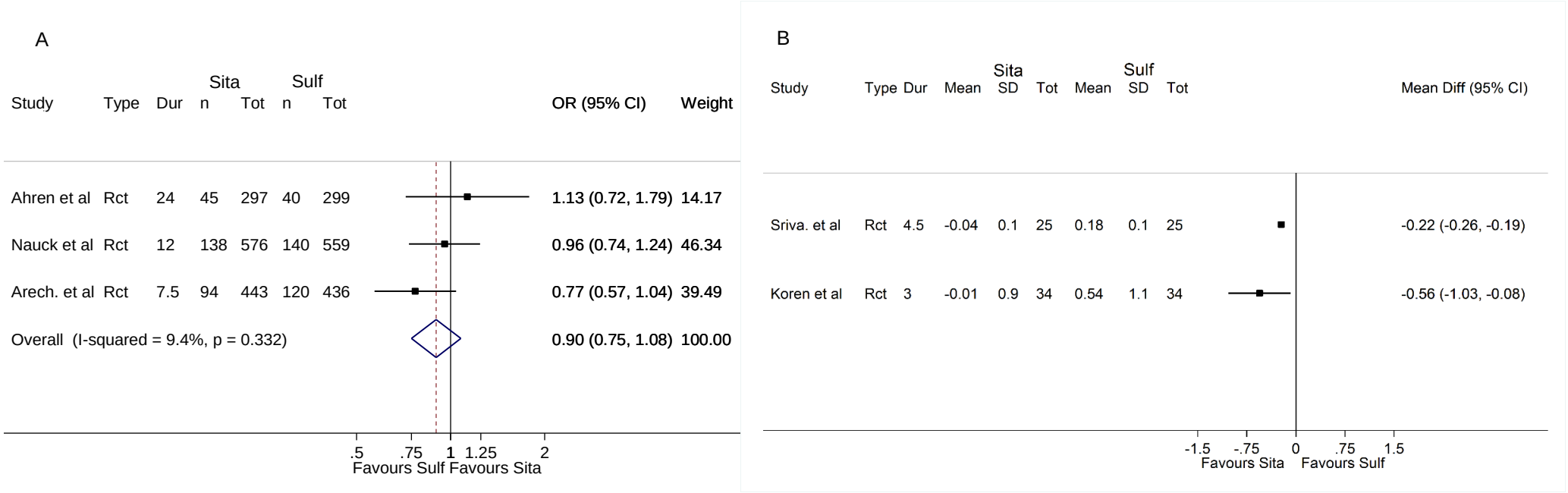
Studies Excluded	Rationale for Exclusion
pre-specified analysis adjusting for the most recently measured HbA1c value[16]	
17. A comparison of the effects of the DPP-4 inhibitor sitagliptin and the sulfonylurea glimepiride on metabolic parameters and endothelial function[17]	Unsuitable comparator – Patients not required to be on metformin.
18. Duration of maintenance of dual therapy with metformin and sitagliptin in type 2 diabetes[18]	Conference abstract only with full study reported elsewhere and included.
19. Comparative Efficacy of Adding Sitagliptin to Metformin, Sulfonylurea or Dual Therapy: A Propensity Score-Weighted Cohort Study[19]	Unsuitable comparator – Comparator involve sitagliptin and sulphonylurea used together not sulphonylurea and metformin.
20. Treatment maintenance duration of dual therapy with metformin and sitagliptin in type 2 diabetes-real-world data from Odyssee study.[20]	Conference abstract only with full study reported elsewhere and included.
21. Assessing time to insulin use among type 2 diabetes patients treated with sitagliptin or sulfonylurea plus metformin dual therapy[21]	Conference abstract only with full study reported elsewhere and included.
22. Clinical efficacy of sitagliptin as add-on to metformin, sulphonylurea or metformin sulphonylurea combined therapy: A propensity score matched cohort study[22]	Unsuitable comparator and Conference abstract only
23. To compare the hypoglycaemic effect of sitagliptin/ metformin combination vs glimepiride in type II diabetes patients during Ramadan[23]	Safety only – hypoglycaemia only outcome reported
24. Sitagliptin more effectively achieves a composite endpoint for A1C reduction, lack of hypoglycaemia and no body weight gain compared with glipizide[24]	Unsuitable composite endpoint reported only
25. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin[25]	Unsuitable comparator of sitagliptin and glimepiride
26. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes[26]	Unsuitable comparator – placebo controlled
27. Diabetes mellitus in the young: Gliptins or sulfonylurea after metformin?[27]	Unclear diagnosis - Patients not confirmed as having Type 2 Diabetes Mellitus and may have any type of diabetes
28. Comparison on adding sitagliptin or glimepiride in poorly controlled overweight type 2 diabetes with oral metformin[28]	Publication only available in Chinese
29. A comparison of glycaemic effects of sitagliptin and sulfonylureas in elderly patients with type 2 diabetes mellitus[29]	Pooled Study of elderly patients from three trials



Supplementary Figure 2A1. Forest Plots comparing sitagliptin and sulphonylureas for HbA1c change (%) from baseline.

Sita=sulphonylureas, Sulf=sulphonylureas, Rct=Randomized controlled trial, Obs=Observational study, Dur=duration in months, SD=Standard deviation, Tot=total participants, Mean Diff=mean difference, NA=not applicable.

Note: Weights where present are from fixed effects meta-analysis though Random-effects estimates were identical and Tau-squared=0% for all meta-analyses



Supplementary Figure 2A2. Forest Plots comparing sitagliptin and sulphonylureas for proportions achieving a HbA1c< 48mmol/mol [<6.5%] at end of study (A) and change in Body Mass Index (kg/m^2) from baseline (B).

Sita=sulphonylureas, Sulf=sulphonylureas Rct=Randomized controlled trial, Obs=Observational study, Dur=duration in months, SD=Standard deviation, Tot=total participants, Mean Diff=mean difference.

Note: Weights where present are from fixed effects meta-analysis though Random-effects estimates were identical.

Supplementary Appraisal 2A1 CASP Appraisal for each included study in Systematic Review

1. Srivastava et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	See Study Characteristics Table
Was assignment of patients to treatments randomised?	Y	Computer generated randomisation
Were all of the patients who entered the trial properly accounted for at its conclusion?	Y	Yes – ITT analysis
Is it worth continuing?	Y	
Were patients, health workers and study personnel blinded to treatment?	N	
Were groups similar at the start of the trial?	Y	No baseline characteristics table provided
Aside from the experimental intervention were groups treated equally?	Y	Yes
What are the main results?		
How large was the treatment effect?	Change in HbA1c from baseline Sita: -0.636 +/-0.99 Sulf: -1.172 +/-0.25 Change in HbA1c shows favourability towards sitagliptin but study was small and possibly underpowered (no details of sample size calculation, power provided and no published protocol)	
How precise was the estimate of the treatment effects?		
Will the results help locally?		
Can results be applied locally?	No	Study population was selected entirely from patients attending a single Hospital in Jaipur in India therefore single centre study in India with few patients which limits generalisability. Study underpowered which also limits applicability.
Were all clinically important outcomes considered?	Yes	Yes, given duration of study of 4.5 months.
Are benefits worth the harms and costs?	CT	Larger, better powered study needed.
Cochrane Bias Assessment Tool	**Results**	**Support for judgement**
Sequence generation adequate	Low	Computerised generated
Allocation concealment	Low	Computerised generated
Blinding to participants/personnel	High	Unblinded to intervention
Blinding to outcome assessors	Low	Adjudicators unblended but as dealing with objective blood results unlikely to bias
Incomplete outcome data	Unc	Not reported on World Health Organisation trial register therefore no idea of low of participants
Selective outcome reporting	Unc	No protocol available to check.
Other sources of bias	High	no baseline characteristics table make it very challenging to interpret results

2. Nauck et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	See Study Characteristics Table
Was assignment of patients to treatments randomised?	Y	Computer generated randomisation
Were all of the patients who entered the trial properly accounted for at its conclusion?	Y	Yes – ITT and PP analysis both reported
Is it worth continuing?	Y	
Were patients, health workers and study personnel blinded to treatment?	Y	
Were groups similar at the start of the trial?	Y	
Aside from the experimental intervention were groups treated equally?	Y	
What are the main results?		
How large was the treatment effect?	Change in HbA1c from baseline Sita: -0.51% (95%CI -0.60 to -0.43) Sulf: -0.56% (95% CI -0.64 to -0.47) Change in HbA1c shows no difference between sitagliptin and sulphonylureas	
How precise was the estimate of the treatment effects?		
Will the results help locally?		
Can results be applied locally?	CT	Multinational and multicentre however the analysis focused on Per-protocol and authors report that a higher number of sitagliptin treated patients discontinued for lack of efficacy. And also that more patients that discontinued had severe hyperglycaemia, overweight and were elderly.
Were all clinically important outcomes considered?	Yes	Yes, given duration of study of 12 months.
Are benefits worth the harms and costs?	Y	Sitagliptin overall seems to produce similar results to sulphonylureas in the majority of patients at least
Cochrane Bias Assessment Tool	**Results**	**Support for judgement**
Sequence generation adequate	Low	Computer generated
Allocation concealment	Low	Computer generated
Blinding to participants/personnel	Low	Double blinded
Blinding to outcome assessors	Low	Double blinded
Incomplete outcome data	Low	As per protocol
Selective outcome reporting	Low	As per protocol
Other sources of bias	Low	

3. Ahren et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	See Study Characteristics Table
Was assignment of patients to treatments randomised?	CT	Not reported but probable
Were all of the patients who entered the trial properly accounted for at its conclusion?	Y	Yes
Is it worth continuing?	Y	
Were patients, health workers and study personnel blinded to treatment?	Y	
Were groups similar at the start of the trial?	Y	
Aside from the experimental intervention were groups treated equally?	Y	
What are the main results?		
How large was the treatment effect?	Change in HbA1c from baseline Sita: -0.28% +/- 1.1 Sulf: -0.31% +/- 1.1 Change in HbA1c shows no difference between sitagliptin and sulphonylureas	
How precise was the estimate of the treatment effects?		
Will the results help locally?		
Can results be applied locally?	CT	Multinational and multicentre however the analysis focused on albiglutide which was the intervention of interest in this study which made certain comparisons more difficult to interpret. Excluded more elderly patients though in general patients were more reflective of "real world" in terms of baseline hba1c and weight
Were all clinically important outcomes considered?	Yes	Yes, given duration of study of 24 months.
Are benefits worth the harms and costs?	Y	Sitagliptin seems to produce similar results to sulphonylureas for primary and secondary outcomes reported
Cochrane Bias Assessment Tool	**Results**	**Support for judgement**
Sequence generation adequate	Unc	Not reported
Allocation concealment	Unc	Not reported
Blinding to participants/personnel	Low	Double blinded
Blinding to outcome assessors	Low	Double blinded
Incomplete outcome data	Low	As per protocol
Selective outcome reporting	Low	As per protocol
Other sources of bias	Low	

4. Kim et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	See Study Characteristics Table
Was assignment of patients to treatments randomised?	CT	Not reported but probable
Were all of the patients who entered the trial properly accounted for at its conclusion?	Y	Yes
Is it worth continuing?	Y	
Were patients, health workers and study personnel blinded to treatment?	Y	
Were groups similar at the start of the trial?	N	Significant imbalance in gender and baseline fasting glucose to name a few. This may be due to fact study was small
Aside from the experimental intervention were groups treated equally?	Y	
What are the main results?		
How large was the treatment effect?	Change in HbA1c from baseline Sita: Baseline: 7.0% +/- 0.5 End: 6.6+/-0.4 Sulf: Baseline: 7.3% +/- 0.4 End: 6.9+/-0.4 Change in HbA1c suggests no difference between sitagliptin and sulphonylureas though no formal analysis undertaken	
How precise was the estimate of the treatment effects?		
Will the results help locally?		
Can results be applied locally?	CT	Study population was selected entirely from patients attending a single Hospital in Seoul in Korea therefore and has only 33 patients which limits generalisability considerably. Study underpowered which also limits applicability.
Were all clinically important outcomes considered?	Yes	Yes, given duration of study of 1 months.
Are benefits worth the harms and costs?	CT	Sitagliptin seems to produce similar results to sulphonylureas which is a novel finding among Korean patients but study was too short and small to conclusively determine this
Cochrane Bias Assessment Tool	**Results**	**Support for judgement**
Sequence generation adequate	Unc	Not reported
Allocation concealment	Unc	Not reported
Blinding to participants/personnel	Low	Double blinded
Blinding to outcome assessors	Low	Double blinded
Incomplete outcome data	Low	As per protocol
Selective outcome reporting	High	Outcomes of interest in the review (hbA1c, Fasting Glucose, cholesterol and triglyceride) are reported incompletely in absolute rather than comparative terms so that they cannot be used for comparative analysis.
Other sources of bias	Low	

5. Seck et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	See Study Characteristics Table
Was assignment of patients to treatments randomised?	Y	Computer generated randomisation
Were all of the patients who entered the trial properly accounted for at its conclusion?	Y	Yes
Is it worth continuing?	Y	
Were patients, health workers and study personnel blinded to treatment?	Y	
Were groups similar at the start of the trial?	Y	
Aside from the experimental intervention were groups treated equally?	Y	
What are the main results?		
How large was the treatment effect?	Change in HbA1c from baseline Sita: -0.33% (95%CI -0.42 to -0.25) Sulf: -0.35% (95% CI -0.44 to -0.26) Change in HbA1c shows no difference between sitagliptin and sulphonylureas	
How precise was the estimate of the treatment effects?		
Will the results help locally?		
Can results be applied locally?	CT	Multinational and multicentre however the analysis focused on per-protocol and authors report that a higher number of sitagliptin treated patients discontinued for lack of efficacy. And also that more patients that discontinued had severe hyperglycaemia, overweight and were elderly.
Were all clinically important outcomes considered?	Yes	Yes, given duration of study of 24 months.
Are benefits worth the harms and costs?	Y	Sitagliptin overall seems to produce similar results to sulphonylureas in the majority of patients at least
Cochrane Bias Assessment Tool	**Results**	**Support for judgement**
Sequence generation adequate	Low	Computer generated
Allocation concealment	Low	Computer generated
Blinding to participants/personnel	Low	Double blinded
Blinding to outcome assessors	Low	Double blinded
Incomplete outcome data	Unc	Less reporting of ITT population and high dropout at 2 year stage made impact of this difficult to interpret
Selective outcome reporting	Low	As per protocol
Other sources of bias	Low	

6. Koren et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	See Study Characteristics Table
Was assignment of patients to treatments randomised?	N	Recruitment order applied to “randomization” which may have negated effect of randomization
Were all of the patients who entered the trial properly accounted for at its conclusion?	Y	Yes
Is it worth continuing?	Y	
Were patients, health workers and study personnel blinded to treatment?	N	Open label
Were groups similar at the start of the trial?	Y	Crossover Trial
Aside from the experimental intervention were groups treated equally?	Y	Crossover Trial
What are the main results?		
How large was the treatment effect?	Change in HbA1c from baseline Sita: - 0.6% +/- 1.1 Sulf: -1.0% +/- 1.1 Change in HbA1c shows no difference between sitagliptin and sulphonylureas	
How precise was the estimate of the treatment effects?		
Will the results help locally?		
Can results be applied locally?	CT	Single centre study with very questionable randomisation and fact study was short with only 37 patients limits generalisability. Study underpowered which also limits applicability however use of crossover trial would have increased power
Were all clinically important outcomes considered?	Yes	Yes, given duration of study of 3 months.
Are benefits worth the harms and costs?	Y	Sitagliptin seems to produce similar results to sulphonylureas which is a novel finding among Korean patients but study was too short and small to conclusively determine this
Cochrane Bias Assessment Tool	**Results**	**Support for judgement**
Sequence generation adequate	High	Questionable randomisation method
Allocation concealment	High	Ordered recruitment may have made allocation obvious
Blinding to participants/personnel	High	Open label
Blinding to outcome assessors	Low	Objective analysis of blood results for outcomes
Incomplete outcome data	Low	
Selective outcome reporting	Low	
Other sources of bias	Low	

7. Arechevelata et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	See Study Characteristics Table
Was assignment of patients to treatments randomised?	Y	
Were all of the patients who entered the trial properly accounted for at its conclusion?	Y	
Is it worth continuing?	Y	
Were patients, health workers and study personnel blinded to treatment?	Y	
Were groups similar at the start of the trial?	Y	
Aside from the experimental intervention were groups treated equally?	Y	
What are the main results?		
How large was the treatment effect?	Change in HbA1c from baseline Sita: -0.46% (95%CI -0.54 to -0.38) Sulf: -0.52% (95% CI -0.60 to -0.45) Change in HbA1c shows no difference between sitagliptin and sulphonylureas	
How precise was the estimate of the treatment effects?		
Will the results help locally?		
Can results be applied locally?	CT	Multinational and multicentre study though baseline hba1c had to be between 6.5 to 9.0 which may have excluded more ill patients biasing results towards patients who were more compliant and better managed. Greater focus on per-protocol results than ITT. Excluded patients from study who failed at several intervals to meet pre-specified glycaemic targets which makes results less reflective of "real world"
Were all clinically important outcomes considered?	Yes	Yes, given duration of study of 7.5 months.
Are benefits worth the harms and costs?	Y	Sitagliptin overall seems to produce similar results to sulphonylureas in the majority of patients at least
Cochrane Bias Assessment Tool	**Results**	**Support for judgement**
Sequence generation adequate	Low	Computer generated
Allocation concealment	Low	Computer generated
Blinding to participants/personnel	Low	Double blinded
Blinding to outcome assessors	Low	Double blinded
Incomplete outcome data	Unc	Inadequate reporting of all outcomes in ITT population, certain outcomes in manuscript reported only for per-protocol population
Selective outcome reporting	Low	
Other sources of bias	Low	

8. Derosa et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	Is efficacy after 5 years of treatment with sitagliptin still maintained?
Was the cohort recruited in an acceptable way?	CT	Recruited from the Dept of Internal Medicine at University of Pavia, Italy prospectively but very strict exclusion criteria and lack of follow up on patients who needed treatment intensification may have made final cohort biased.
Is it worth continuing?	Y	
Was the exposure accurately measured to minimised bias?	Y	Prospectively measured and monitored
Was the outcome accurately measured to minimise bias?	Y	Yes, hba1c is an objective blood results measurement reflecting glycaemic control in diabetes
Have the authors identified all important confounding factors?	CT	The authors matched for age, sex, diabetes duration which ae important. There are a multitude of additional variables that the authors could have considered relating to diet and socioeconomic status, concomitant medication: steroids, antipsychotics and comorbidities e.g. thyroid disease the authors might have considered. However given quite strict exclusion criteria and the information though limited in baseline characteristics, the groups were possible well matched. The authors were more interested in efficacy than effectiveness.
Have they taken account of the confounding factors in design/analysis?	CT	As above
Was the follow up of subjects complete enough?	N	Though follow up was up to 5 years, no reporting of how many patients actually completed and withdrew from the study over this period which is likely to have been substantial.
Was the follow up of subjects long enough?	Y	5 years would make it longest cohort study undertaken addressing this question
What are the results?		
What are the main results of the study?	Change in HbA1c from baseline Sita: Baseline: 8.3% +/- 0.3 End: 6.4+/-0.7 Sulf: Baseline: 8.5% +/- 0.5 End: 7.8+/-0.2 No statistical analysis and thus no confidence intervals are presented. On a purely qualitative level, the sitagliptin patients appear to perform better over the 5 year period but without taking into account confounders and a proper multivariate analysis it is difficult to judge.	
How precise was the estimate of the treatment effects?		
Do you believe the results?	CT	As no analysis presented, only baseline and final hba1c, fasting glucose and BMI values. Plausible results
Will the results help locally?	CT	
Can results be applied locally?	CT	Single centre prospective cohort study in Italy using "real world" patients however the very strict exclusion criteria and the exclusion from follow up of patients that needed treatment intensification, make the study less informative. Also no statistical analysis is presented and therefore very hard to interpret the results in detail.
Do the results fit with other available evidence?	CT	This is one of the first studies to examine efficacy at 5years therefore it is difficult to answer as no frame of reference.
What are the implications of this study for practice?	CT	More studies of longer duration still needed as the analysis was inadequate in study and several longer term microvascular and macrovascular complications which might have been addressed in such a long term study could not due to a lack of funding to investigate these in the protocol.
Newcastle Ottawa Scale	**Results**	**Support for judgement**
Selection (max 4 stars)	* * *	The cohort was selected from a single centre, Italian hospital and very strict exclusion criteria was applied

		removing the most ill patients. This made this study less representative. The comparator cohort, exposure and outcome selections were adequate.
Comparability (max 2 stars)	*	Matched for age, sex and diabetes duration but several confounding factors possibly ignored and no detailed analysis provided for final results.
Outcome (max 3 stars)	**	Long follow up planned, and objective outcome but significantly inadequate reporting of number of subjects lost to follow up. This loss may have biased results but as not reported cannot be sure.
Overall Evidence Quality Rating	Low	

9. Valensi et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	Treatment maintenance duration with sitagliptin vs metformin?
Was the cohort recruited in an acceptable way?	Y	Multicentre study with recruitment spread throughout 1569 general practices in France shown to be representative of typical general practices in France.
Is it worth continuing?	Y	
Was the exposure accurately measured to minimised bias?	Y	Prospectively measured and monitored
Was the outcome accurately measured to minimise bias?	Y	Yes, patients monitored for minimum of 36 months with little drop out with regards primary outcome.
Have the authors identified all important confounding factors?	Y	The authors incorporate several design features to minimise bias and account for confounders 1. Physicians were asked to enrol patients that were deemed by their judgement equally eligible for sitagliptin or sulphonylurea 2. Propensity Score was generated using a broad range of demographic, comorbidity and treatment confounders and used to adjust final analysis 3. Time varying confounders which may have introduced bias after study initiation were also analysed 4. Several sensitivity analysis were conducted exploring impact of missing data reported in Appendix
Have they taken account of the confounding factors in design/analysis?	CT	As above
Was the follow up of subjects complete enough?	N	Yes with flow of participants clearly displayed
Was the follow up of subjects long enough?	Y	
What are the results?		
What are the main results of the study?	Number of individuals requiring treatment change Sita: 621 of 1874 needed treatment change Sulf: 341 of 733 needed treatment change Hazard Ratio 0.65 (95% CI 0.57-0.73) Significantly fewer participants on sitagliptin required a treatment changed than those on sulphonylureas. The only limitation with interpretation was that this was a patient/physician determined treatment change and hence was not objective. They could also have included a HbA1c threshold to indicate a need for treatment change which would have made outcome more objective. However overall quite co	
How precise was the estimate of the treatment effects?		
Do you believe the results?	Y	Overall the results are credible due to a robust method and analysis. The only limitation with interpretation of the outcome was that this was a patient/physician determined treatment change and hence was not objective. They could also have included a hbA1c threshold to indicate a need for treatment change which would have made outcome more objective. However overall quite confident in results.
Will the results help locally?	Y	
Can results be applied locally?	Y	Multicentre, well analysed and presented study with a useful “real world” outcome reflecting a need for treatment change. The fact that fewer patients changed on sitagliptin compared to sulphonylureas suggests greater patient/physician satisfaction of the drug.
Do the results fit with other available evidence?	CT	First study of its kind
What are the implications of this study for practice?	Y	This study provides convincing evidence that sitagliptin is a more successful medication in terms of

		physician and patients' satisfaction than sulphonylureas. It does however miss an objective measure of success which would have made the study even more useful e.g. number maintaining hba1c<7.0% throughout study
Newcastle Ottawa Scale	**Results**	**Support for judgement**
Selection (max 4 stars)	* * * *	The cohort was selected from over 1569 practice throughout France shown to be representative in terms of age and gender for France. Exposure and Outcome was ascertained prospectively
Comparability (max 2 stars)	**	Excellent use of prospective design, propensity scores and sensitivity analysis to minimise bias risk related to confounding and missing data
Outcome (max 3 stars)	****	Clearly reported follow up of 36 months or greater with flow of participants and assessment and analysis of outcome well described.
Overall Evidence Quality Rating	High	

10. Inzucchi et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	Risk of insulin initiation
Was the cohort recruited in an acceptable way?	Y	Multicentre retrospective cohort study including eligible patients from across 49 US states using GE Centricity electronic medical records.
Is it worth continuing?	Y	
Was the exposure accurately measured to minimised bias?	Y	Yes, measured using prescription records though of course it is more challenging to tell if patient took medication as prescribed in a retrospective study
Was the outcome accurately measured to minimise bias?	Y	Yes, patients followed until insulin initiation as measured by prescription issue or until end of data collection period.
Have the authors identified all important confounding factors?	Y	The authors incorporate several design features to minimise bias and account for confounders 1. Large sample size from large database 2. Successful propensity Score matching analysis to ensure more accurate comparison. 3. Appropriate prespecified sensitivity analysis conducted exploring impact of missing data and subgroups
Have they taken account of the confounding factors in design/analysis?	Y	Broad range of confounders used. Prop score matching shows that standardised mean difference were not statistically significant after matching.
Was the follow up of subjects complete enough?	Y	Right censoring was significant though and may have biased analysis though very difficult to say.
Was the follow up of subjects long enough?	Y	Attempted to follow up individuals for 72 months or till insulin initiation as per study protocol.
What are the results?		
What are the main results of the study? How precise was the estimate of the treatment effects?	Number of individuals initiating insulin Sita: 1028 of 3864 needed treatment change Sulf: 1318 of 3864 needed treatment change Hazard Ration 0.76 (95% CI 0.65-0.90) Significantly fewer participants on sitagliptin (24% less) were initiated on insulin during follow up compared to sulphonylureas. The only limitation with this was the significant amount of right censoring though authors claim they did several sensitivity analysis (not reported) and lack of secondary care data available means that if insulin had been initiated in hospital it may have been missed. The argument may be that this should theoretically bias both sitagliptin and sulphonylurea arms equally but not reported.	
Do you believe the results?	Y	Overall the results are credible due to a robust method and analysis as well as good sample size for study
Will the results help locally?	Y	
Can results be applied locally?	Y	Multicentre, well analysed and presented study with a useful "real world" outcome reflecting the need for insulin initiation among patients with diabetes. The fact that fewer patients changed on sitagliptin compared to sulphonylureas suggests greater patient/physician satisfaction and success with the drug. The authors do comment that the database does over represent an older population who have commercial insurance and reside in northeaster and Midwestern US states however. Though impact of this is difficult to assess.
Do the results fit with other available evidence?	Y	In general previous studies have showed that sulphonylurea patients do progress to insulin faster with other DPP-4 inhibitors as well as other comparators.
What are the implications of this study for practice?	Y	This study provides convincing evidence that sitagliptin is a more successful medication in terms of delaying insulin initiation. Though useful insulin is

		associated with hypoglycaemia, weight gain and increases complexity of care in general.
Newcastle Ottawa Scale	**Results**	**Support for judgement**
Selection (max 4 stars)	* * * *	The cohort was selected from a database storing electronic medical records from across 49 US states practice throughout France shown to be representative in t. Exposure and Outcome was ascertained similarly using prescription records retrospectively based on continuous prescription issue over 90 days.
Comparability (max 2 stars)	**	Excellent use of propensity scores and sensitivity analysis to minimise bias risk related to confounding and missing data. Still a risk of bias from missing hospital data though this may potentially balance out across both arms.
Outcome (max 3 stars)	****	Clearly reported follow up of 72 months with number of patients eligible for analysis at each timepoint. Right censoring was extensive which is discussed in detail in manuscript but given the authors have used a survival analysis to analyse the data, it is assumed they considered any censoring to be random rather than actually related to the study drugs.
Overall Evidence Quality Rating	High	

11. Ki lee et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	Change in HbA1c after 24 weeks from baseline
Was the cohort recruited in an acceptable way?	Y	Recruited from a Single Centre in Korea prospectively but quite strict exclusion criteria and significant loss to follow (14.7%) up for small and short study.
Is it worth continuing?	Y	
Was the exposure accurately measured to minimised bias?	Y	Prospectively measured and monitored
Was the outcome accurately measured to minimise bias?	Y	Yes, hba1c is an objective blood results measurement reflecting glycaemic control in diabetes
Have the authors identified all important confounding factors?	CT	The authors demonstrate that baseline characteristics were well matched and adjust for baseline age, sex, hba1c and metformin dose which are all appropriate however they may have missed certain relevant comorbidities and concomitant medications as well (though most of these patients may have been excluded by strict exclusion criteria)
Have they taken account of the confounding factors in design/analysis?	CT	As above
Was the follow up of subjects complete enough?	N	Though follow up was up to 6 months and there is reporting of how many patients actually completed and withdrew from the study over this period, this was substantial at 14.6% for a relatively short study.
Was the follow up of subjects long enough?	Y	
What are the results?		
What are the main results of the study?	Change in HbA1c from baseline Sita: Baseline: 9.3% (IQR 7.8 to 10.4) to End: 6.3%(IQR 6.0 to 6.7) Wilcoxon sign rank test: p<0.001 Sulf: Baseline: 8.9% (IQR 8.2 to 10.3) to End: 6.4%(IQR 6.0 to 6.7) Wilcoxon sign rank test: p<0.001 Both reductions were similar and significant in HbA1c and after adjustment there was no significant difference observed between treatments.	
How precise was the estimate of the treatment effects?		
Do you believe the results?	Y	Similar to other studies of similar duration
Will the results help locally?	Y	
Can results be applied locally?	Y	Single centre prospective cohort study in Korea using "real world" patients however the very strict exclusion criteria and high loss to follow up make the study less informative. Useful to inform efficacy in Korean patients specifically
Do the results fit with other available evidence?	Y	Similar results to other studies of similar duration
What are the implications of this study for practice?		Useful for Korean physicians to demonstrate equal glycaemic efficacy for metformin and sitagliptin to metformin and sulphonylureas
Newcastle Ottawa Scale	**Results**	**Support for judgement**
Selection (max 4 stars)	* * *	The cohort was selected from a single centre in Korea and very strict exclusion criteria was applied removing the most ill patients. This made this cohort less representative. The comparator cohort was however selected similarly and exposure and outcome selections were adequate.
Comparability (max 2 stars)	**	Adjusted for age, sex, BMI and metformin dose but several confounding factors possibly ignored such as comorbidities but given strict exclusion criteria this may not be significant.
Outcome (max 3 stars)	**	Significant number of subjects lost to follow up for a small study of short duration. This loss may have biased results.

Overall Evidence Quality Rating	Moderate	

12. Suraj et al		
CASP TOOL	**Answer**	**Comment**
Are results of trial valid?	Y	
Did Trial address a clearly focused Issue?	Y	Change in HbA1c after 12 weeks from baseline
Was the cohort recruited in an acceptable way?	Y	Recruited from a Single Centre in New Delhi, India prospectively but relatively strict exclusion criteria.
Is it worth continuing?	Y	
Was the exposure accurately measured to minimised bias?	Y	Prospectively measured and monitored
Was the outcome accurately measured to minimise bias?	Y	Yes, hba1c is an objective blood results measurement reflecting glycaemic control in diabetes
Have the authors identified all important confounding factors?	N	The authors demonstrate that baseline characteristics were only reasonably matched and do not present any adjustments even for basic variables such as baseline age, sex, hba1c and metformin dose. In addition there may be other relevant confounders too such as concomitant medications and certain comorbidities as well (though most of these patients may have been excluded by strict exclusion criteria)
Have they taken account of the confounding factors in design/analysis?	N	As above
Was the follow up of subjects complete enough?	N	This was a short 12 week study with a small sample size. 150 of 187 patients recruited completed the stud. Those lost to follow up are not explained in a flow diagram
Was the follow up of subjects long enough?	CT	Most likely not, sulphonylurea efficacy has been well established as peaking within first 3 months in every study before it levels off. This study produces results that make sulphonylurea look favourable but it is most likely due to a combination of this effect and lack of adjustment for confounders
What are the results?		
What are the main results of the study?	Change in HbA1c from baseline Sita: -0.70% +/- 0.83 Sulf: -1.19% +/- 0.67 P<0.001 for difference 95%CI(0.16,0.82) Change in HbA1c is greater with sulphonylureas based on statistical test above which appears to be a T-test though not confirmed in manuscript. They do not appear to have adjusted for any confounders which makes interpretation more challenging.	
How precise was the estimate of the treatment effects?		
Do you believe the results?	CT	Similar to other studies of similar duration in terms of sulphonylureas peaking in effect within first 3 months however lack of adjustment for confounders
Will the results help locally?	CT	
Can results be applied locally?	N	Single centre prospective cohort study in India using “real world” patients however the very strict exclusion criteria, high loss to follow up, short duration and lack of adjustment of confounders makes results less useful
Do the results fit with other available evidence?	Y	Similar results to other studies of similar duration
What are the implications of this study for practice?		Useful for Indian physicians to demonstrate glycaemic efficacy for sulphonylureas, but the significant peak with sulphonylureas is most likely due to the short duration of the study and the lack of confounder adjustment and hence may be misleading
Newcastle Ottawa Scale	**Results**	**Support for judgement**
Selection (max 4 stars)	* * *	The cohort was selected from a single centre in India and very strict exclusion criteria was applied removing the most ill patients. This made this cohort less representative. The comparator cohort was

		however selected similarly and exposure and outcome selections were adequate.
Comparability (max 2 stars)		Adjusted for age, sex, BMI and metformin dose but several confounding factors possibly ignored such as comorbidities but given strict exclusion criteria this may not be significant.
Outcome (max 3 stars)	*	Outcome assessment was an objective hbA1c measurement, but significant number of subjects lost to follow up for a small study, possibly too short a study duration exacerbated by lack of adjustment for confounders. This may have biased results.
Overall Evidence Quality Rating	Low	

Supplementary References 2A1

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Appendix B. **Supplementary Material for Chapter 4**

Supplementary Table 4A1 Read Code List used to identify individuals with diabetes mellitus

Code-type	Description	Read code
1	type i diabetes mellitus with gangrene	C10E611
1	type i diabetes mellitus with renal complications	C108011
1	unstable insulin dependent diabetes mellitus	C10E412
1	unstable type i diabetes mellitus	C108411
1	type 1 diabetes mellitus without complication	C10EA00
1	type i diabetes mellitus with peripheral angiopathy	C108G11
1	insulin dependent diabetes mellitus with hypoglycaemi	C10EE12
1	type i diabetes mellitus with ketoacidotic coma	C10EN11
1	type i diabetes mellitus with polyneuropathy	C108C11
1	insulin dependent diabetes mellitus with arthropathy	C108H00
1	insulin dependent diab mell with neuropathic arthropa	C10EJ12
1	insulin dependent diabetes mellitus with polyneuropat	C10EC12
1	insulin dependent diabetes mellitus with nephropathy	C108D00
1	unstable type 1 diabetes mellitus	C108412
1	diabetes mellitus, juvenile type, with ketoacidosis	C101000
1	type i diabetes mellitus with neuropathic arthropathy	C10EJ11
1	diabetes mellitus, juvenile type, with hyperosmolar c	C102000
1	type 1 diabetes mellitus with neuropathic arthropathy	C108J12
1	type 1 diabetes mellitus without complication	C108A12
1	type 1 diabetes mellitus with ulcer	C10E500
1	type i diabetes mellitus with ketoacidosis	C10EM11
1	type 1 diabetes mellitus with hypoglycaemic coma	C108E12
1	type i diabetes mellitus with diabetic cataract	C10EF11
1	insulin dependent diabetes mellitus with polyneuropat	C108C00
1	type 1 diabetes mellitus with polyneuropathy	C108C12
1	type 1 diabetes mellitus with gangrene	C108612
1	type i diabetes mellitus - poor control	C108811
1	type 1 diabetes mellitus with diabetic cataract	C108F12
1	pre-existing diabetes mellitus, insulin-dependent	L180500
1	insulin dependent diab mell with peripheral angiopath	C108G00
1	insulin dependent diabetes mellitus with ulcer	C108500
1	insulin dependent diabetes mellitus with mononeuropat	C10EB12
1	type 1 diabetes mellitus with hypoglycaemic coma	C10EE00
1	insulin dependent diabetes mellitus	C10E.12
1	type i diabetes mellitus with ulcer	C10E511
1	insulin dependent diabetes mellitus with multiple com	C10E312
1	type 1 diabetes mellitus maturity onset	C108912
1	iddm-insulin dependent diabetes mellitus	C108.11
1	type 1 diabetes mellitus maturity onset	C10E900
1	type i diabetes mellitus	C10E.11
1	insulin dependent diabetes mellitus with multiple com	C108300
1	type 1 diabetes mellitus with arthropathy	C10EH00

Code-type	Description	Read code
1	insulin dependent diab mell with peripheral angiopath	C10EG12
1	diabetes mellitus, juvenile type, with ketoacidotic c	C103000
1	insulin-dependent diabetes mellitus with neurological	C108200
1	type i diabetes mellitus with mononeuropathy	C10EB11
1	type i diabetes mellitus with persistent proteinuria	C10EK11
1	type 1 diabetes mellitus with persistent microalbumin	C10EL00
1	insulin dependent diabetes mellitus - poor control	C108800
1	type 1 diabetes mellitus - poor control	C108812
1	unstable insulin dependent diabetes mellitus	C108400
1	type 1 diabetes mellitus with neurological complicati	C10E200
1	insulin-dependent diabetes mellitus with neurological	C10E212
1	type i diabetes mellitus with gangrene	C108611
1	type i diabetes mellitus with retinopathy	C108711
1	type i diabetes mellitus - poor control	C10E811
1	diabetes mellitus, juvenile type, no mention of compl	C100000
1	iddm with peripheral circulatory disorder	C107300
1	type 1 diabetes mellitus - poor control	C10E800
1	insulin dependent diabetes mellitus with gangrene	C10E612
1	type 1 diabetes mellitus	C10E.00
1	type 1 diabetes mellitus with nephropathy	C108D12
1	diabetes mellitus, juvenile +peripheral circulatory d	C107000
1	type i diabetes mellitus with nephropathy	C108D11
1	insulin dependent diabetes maturity onset	C108900
1	diabetes type 1 review	66An.00
1	diet advice for insulin-dependent diabetes	ZC2C911
1	type i diabetes mellitus with diabetic cataract	C108F11
1	insulin dependent diab mell with neuropathic arthropa	C108J00
1	type 1 diabetes mellitus with mononeuropathy	C108B12
1	type 1 diabetes mellitus with nephropathy	C10ED00
1	unstable type i diabetes mellitus	C10E411
1	insulin dependent diabetes mellitus with diabetic cat	C108F00
1	insulin dependent diabetes mellitus with mononeuropat	C108B00
1	insulin dependent diabetes mellitus with diabetic cat	C10EF12
1	type 1 diabetes mellitus with gastroparesis	C10EQ00
1	type 1 diabetes mellitus with ophthalmic complication	C10E100
1	insulin dependent diabetes mellitus with retinopathy	C10E712
1	type 1 diabetes mellitus with polyneuropathy	C10EC00
1	diabetes mellitus, juvenile type, with renal manifest	C104000
1	type 1 diabetes mellitus with ketoacidosis	C10EM00
1	type i diabetes mellitus with gastroparesis	C10EQ11
1	insulin dependent diabetes mellitus	C100011
1	insulin dependent diabetes mellitus with arthropathy	C10EH12
1	dietary advice for type i diabetes	ZC2C900
1	type i diabetes mellitus with exudative maculopathy	C10EP11
1	type i diabetes mellitus with peripheral angiopathy	C10EG11

Code-type	Description	Read code
1	type 1 diabetes mellitus with renal complications	C10E000
1	type 1 diabetes mellitus with ketoacidotic coma	C10EN00
1	type 1 diabetes mellitus with arthropathy	C108H12
1	type 1 diabetes mellitus	C108.12
1	diabetes mellitus, juvenile, + other specified manife	C10y000
1	insulin dependent diabetes maturity onset	C10E912
1	type 1 diabetic dietary review	66At011
1	type i diabetes mellitus maturity onset	C108911
1	type i diabetes mellitus without complication	C108A11
1	insulin dependent diabetes mellitus with gangrene	C108600
1	type i diabetes mellitus with renal complications	C10E011
1	diabetes mellitus, juvenile type, + unspecified compl	C10z000
1	type 1 diabetes mellitus with multiple complications	C108312
1	type i diabetes mellitus with multiple complications	C108311
1	insulin dependent diabetes mellitus with ulcer	C10E512
1	insulin-dependent diabetes without complication	C10EA12
1	type i diabetes mellitus	C108.13
1	type i diabetes mellitus with persistent microalbumin	C10EL11
1	type 1 diabetes mellitus with retinopathy	C10E700
1	type i diabetes mellitus with multiple complications	C10E311
1	type i diabetes mellitus with arthropathy	C108H11
1	type 1 diabetes mellitus with persistent proteinuria	C10EK00
1	insulin dependent diabetes mellitus	C108.00
1	type i diabetes mellitus maturity onset	C10E911
1	type i diabetes mellitus with polyneuropathy	C10EC11
1	perceived control of insulin-dependent diabetes	ZRbH.00
1	type i diabetes mellitus with retinopathy	C10E711
1	insulin-dependent diabetes mellitus with renal compli	C10E012
1	type i diabetes mellitus with hypoglycaemic coma	C108E11
1	type i diabetes mellitus with neurological complicati	C108211
1	type 1 diabetes mellitus with neurological complicati	C108212
1	type 1 diabetes mellitus with retinopathy	C108712
1	type i diabetes mellitus with mononeuropathy	C108B11
1	type i diabetic dietary review	66At000
1	type i diabetes mellitus with arthropathy	C10EH11
1	insulin-dependent diabetes mellitus with renal compli	C108000
1	type i diabetes mellitus with neurological complicati	C10E211
1	type i diabetes mellitus with ophthalmic complication	C108111
1	insulin-dependent diabetes mellitus with ophthalmic c	C10E112
1	type 1 diabetes mellitus with diabetic cataract	C10EF00
1	type 1 diabetes mellitus with gangrene	C10E600
1	insulin-dependent diabetes mellitus with ophthalmic c	C108100
1	type i diabetes mellitus with neuropathic arthropathy	C108J11
1	insulin-dependent diabetes without complication	C108A00
1	insulin dependent diabetes mellitus with retinopathy	C108700

Code-type	Description	Read code
1	type 1 diabetes mellitus with ulcer	C108512
1	insulin dependent diabetes mellitus - poor control	C10E812
1	type 1 diabetes mellitus with peripheral angiopathy	C108G12
1	type i diabetes mellitus with nephropathy	C10ED11
1	type 1 diabetes mellitus with peripheral angiopathy	C10EG00
1	type i diabetes mellitus without complication	C10EA11
1	insulin dependent diabetes mellitus with hypoglycaemi	C108E00
1	type i diabetes mellitus with ulcer	C108511
1	diabetes mellitus, juvenile, + neurological manifesta	C106000
1	type 1 diabetes mellitus with neuropathic arthropathy	C10EJ00
1	type i diabetes mellitus with ophthalmic complication	C10E111
1	type 1 diabetes mellitus with multiple complications	C10E300
1	type i diabetes mellitus with hypoglycaemic coma	C10EE11
1	type 1 diabetes mellitus with exudative maculopathy	C10EP00
1	insulin dependent diabetes mellitus with nephropathy	C10ED12
1	diabetes mellitus, juvenile type, + ophthalmic manife	C105000
1	type 1 diabetes mellitus with ophthalmic complication	C108112
1	unstable type 1 diabetes mellitus	C10E400
1	type 1 diabetes mellitus with mononeuropathy	C10EB00
1	type 1 diabetes mellitus with renal complications	C108012
2	type ii diabetes mellitus with hypoglycaemic coma	C109D11
2	type 2 diabetes mellitus - poor control	C10F700
2	type 2 diabetes mellitus - poor control	C109712
2	type 2 diabetes mellitus with renal complications	C10F000
2	diabetic on diet only	66A3.00
2	non-insulin dependent diabetes mellitus with nephropa	C109C00
2	type ii diabetic dietary review	66At100
2	non-insulin dependent diabetes mellitus with ulcer	C109400
2	insulin treated type ii diabetes mellitus	C10FJ11
2	type ii diabetes mellitus with ulcer	C10F411
2	non-insulin-dependent diabetes mellitus with multiple	C109300
2	non-insulin-dependent diabetes mellitus with ophthalm	C109100
2	type 2 diabetes mellitus without complication	C109912
2	insulin treated non-insulin dependent diabetes mellit	C109J11
2	type ii diabetes mellitus - poor control	C10F711
2	non-insulin dependent diabetes mellitus with polyneur	C109B00
2	type ii diabetes mellitus with ophthalmic complicatio	C109111
2	type 2 diabetes mellitus with diabetic cataract	C109E12
2	type ii diabetes mellitus with mononeuropathy	C10FA11
2	type 2 diabetes mellitus with multiple complications	C10F300
2	insulin treated type 2 diabetes mellitus	C10FJ00
2	type ii diabetes mellitus with gangrene	C109511
2	type 2 diabetes mellitus with gastroparesis	C10FR00
2	hyperosmolar non-ketotic state in type ii diabetes me	C10FK11
2	type 2 diabetes mellitus with ketoacidotic coma	C10FP00

Code-type	Description	Read code
2	niddm - non-insulin dependent diabetes mellitus	C109.11
2	dietary advice non-insulin-dependent diabetes	ZC2CA11
2	non-insulin dependent diabetes mellitus with gangrene	C109500
2	hyperosmolar non-ketotic state in type 2 diabetes mel	C10FK00
2	type ii diabetes mellitus with neurological complicat	C109211
2	type ii diabetes mellitus with neuropathic arthropath	C109H11
2	type 2 diabetes mellitus with ulcer	C109412
2	type ii diabetes mellitus with ulcer	C109411
2	diabetes mellitus, adult, + peripheral circulatory di	C107100
2	type 2 diabetes mellitus with neuropathic arthropathy	C109H12
2	type 2 diabetes mellitus with diabetic cataract	C10FE00
2	type 2 diabetes mellitus with hypoglycaemic coma	C10FD00
2	type 2 diabetes mellitus with retinopathy	C109612
2	pre-existing diabetes mellitus, non-insulin-dependent	L180600
2	diabetes mellitus, adult, + other specified manifesta	C10y100
2	type ii diabetes mellitus with exudative maculopathy	C10FQ11
2	insulin treated type 2 diabetes mellitus	C109J00
2	type 2 diabetes mellitus with polyneuropathy	C109B12
2	type ii diabetes mellitus with neuropathic arthropath	C10FH11
2	type 2 diabetes mellitus with arthropathy	C109G12
2	type 2 diabetes mellitus with exudative maculopathy	C10FQ00
2	type 2 diabetes mellitus with polyneuropathy	C10FB00
2	type 2 diabetes mellitus with renal complications	C109012
2	non-insulin-dependent diabetes mellitus with retinopa	C109600
2	type ii diabetes mellitus with polyneuropathy	C109B11
2	non-insulin dependent diabetes mellitus with hypoglyc	C109D00
2	type 2 diabetes mellitus with peripheral angiopathy	C109F12
2	type ii diabetes mellitus with ophthalmic complicatio	C10F111
2	type 2 diabetes mellitus with nephropathy	C10FC00
2	non-insulin dependent diabetes mellitus	C109.00
2	type 2 diabetes mellitus with persistent microalbumin	C10FM00
2	type 2 diabetes mellitus with ophthalmic complication	C10F100
2	type ii diabetes mellitus - poor control	C109711
2	diabetic on oral treatment	66A4.00
2	type 2 diabetes mellitus with gangrene	C109512
2	insulin treated type ii diabetes mellitus	C109J12
2	type 2 diabetes mellitus with hypoglycaemic coma	C109D12
2	type ii diabetes mellitus with mononeuropathy	C109A11
2	dietary advice for type ii diabetes	ZC2CA00
2	diabetes mellitus, adult onset, with hyperosmolar com	C102100
2	type 2 diabetes mellitus with ophthalmic complication	C109112
2	diabetes type 2 review	66Ao.00
2	type ii diabetes mellitus with diabetic cataract	C10FE11
2	non-insulin-dependent diabetes mellitus without compl	C109900
2	type ii diabetes mellitus with ketoacidotic coma	C10FP11

Code-type	Description	Read code
2	diabetes mellitus, adult onset, no mention of complic	C100100
2	type 2 diabetes mellitus with ketoacidosis	C10FN00
2	type 2 diabetes mellitus with ulcer	C10F400
2	type ii diabetes mellitus with nephropathy	C109C11
2	type ii diabetes mellitus with peripheral angiopathy	C10FF11
2	type ii diabetes mellitus with neurological complicat	C10F211
2	type ii diabetes mellitus	C109.13
2	type 2 diabetes mellitus with persistent proteinuria	C10FL00
2	non-insulin dependent diabetes mellitus	C100112
2	type ii diabetes mellitus with gastroparesis	C10FR11
2	type ii diabetes mellitus with nephropathy	C10FC11
2	non-insulin-dependent d m with peripheral angiopath	C109F00
2	non-insulin-dependent diabetes mellitus with renal co	C109000
2	type 2 diabetes mellitus with neurological complicati	C10F200
2	non-insulin depend diabetes mellitus with diabetic ca	C109E00
2	type 2 diabetic dietary review	66At111
2	diabetes mellitus, adult onset, + unspecified complic	C10z100
2	type 2 diabetes mellitus	C109.12
2	type ii diabetes mellitus with renal complications	C109011
2	maturity onset diabetes	C100111
2	type 2 diabetes mellitus with peripheral angiopathy	C10FF00
2	type 2 diabetes mellitus with multiple complications	C109312
2	diabetes mellitus, adult onset, + neurological manife	C106100
2	type ii diabetes mellitus with retinopathy	C109611
2	type ii diabetes mellitus without complication	C10F911
2	type 2 diabetes mellitus without complication	C10F900
2	type ii diabetes mellitus with retinopathy	C10F611
2	non-insulin dependent diabetes mellitus with mononeur	C109A00
2	niddm with peripheral circulatory disorder	C107400
2	type 2 diabetes mellitus with retinopathy	C10F600
2	non-insulin dependent d m with neuropathic arthropath	C109H00
2	type ii diabetes mellitus with multiple complications	C109311
2	type 2 diabetes mellitus	C10F.00
2	type ii diabetes mellitus	C10F.11
2	type ii diabetes mellitus with arthropathy	C109G11
2	type ii diabetes mellitus with diabetic cataract	C109E11
2	type ii diabetes mellitus with hypoglycaemic coma	C10FD11
2	type ii diabetes mellitus with multiple complications	C10F311
2	type 2 diabetes mellitus with mononeuropathy	C10FA00
2	type 2 diabetes mellitus with arthropathy	C10FG00
2	type 2 diabetes mellitus with neurological complicati	C109212
2	non-insulin dependent diabetes mellitus - poor contro	C109700
2	type ii diabetes mellitus with polyneuropathy	C10FB11
2	diabetes mellitus, adult onset, with renal manifestat	C104100
2	type 2 diabetes mellitus with neuropathic arthropathy	C10FH00

Code-type	Description	Read code
2	type ii diabetes mellitus with ketoacidosis	C10FN11
2	diabetes mellitus, adult with gangrene	C107200
2	diabetes mellitus autosomal dominant type 2	C10D.00
2	type ii diabetes mellitus with persistent proteinuria	C10FL11
2	hyperosmolar non-ketotic state in type 2 diabetes mel	C109K00
2	type ii diabetes mellitus with gangrene	C10F511
2	type 2 diabetes mellitus with gangrene	C10F500
2	non-insulin-dependent diabetes mellitus with neuro co	C109200
2	type ii diabetes mellitus with arthropathy	C10FG11
2	diabetes mellitus, adult onset, + ophthalmic manifest	C105100
2	non-insulin dependent diabetes mellitus with arthropa	C109G00
2	type ii diabetes mellitus with persistent microalbumi	C10FM11
2	type 2 diabetes mellitus with mononeuropathy	C109A12
2	type ii diabetes mellitus without complication	C109911
2	type ii diabetes mellitus with peripheral angiopathy	C109F11
2	type 2 diabetes mellitus with nephropathy	C109C12
2	type ii diabetes mellitus with renal complications	C10F011
Unclear	csq - diabetes clinic satisfaction questionnaire	ZRB4.11
Unclear	o/e - left diabetic foot at risk	2G5B.00
Unclear	diabetic retinopathy screening not indicated	8I6F.00
Unclear	diabetic diet - poor compliance	66Aa.00
Unclear	o/e - left eye background diabetic retinopathy	2BBQ.00
Unclear	excluded from diabetic retinopathy screening as decea	9m06.00
Unclear	chronic painful diabetic neuropathy	F372100
Unclear	diabetic retinopathy nos	F420z00
Unclear	diabetes mellitus with neurological manifestation	C106.00
Unclear	diabetes mellitus with ketoacidosis	C101.00
Unclear	patient held diabetic record issued	9360.00
Unclear	diabetes wellbeing questionnaire	ZRB6.00
Unclear	o/e - diabetic maculopathy present both eyes	2BBL.00
Unclear	excluded from diabetic retinopathy screen physical di	9m0E.00
Unclear	has seen dietician - diabetes	66A8.00
Unclear	referral to diabetic register	8HHy.00
Unclear	diabetic charcot arthropathy	N030100
Unclear	referral for diabetic retinopathy screening	8Hl1.00
Unclear	referral to diabetes nurse	ZL62500
Unclear	other specified diabetes mellitus with periph circ co	C107y00
Unclear	o/e - left diabetic foot at low risk	2G5I.00
Unclear	dietary advice for diabetes mellitus	ZC2C800
Unclear	diabetic dietary review	66At.00
Unclear	diabetic polyneuropathy	F372.11
Unclear	malnutrition-related diabetes mellitus with multiple	C10A600
Unclear	mixed diabetic ulcer - foot	M271200
Unclear	fundoscopy - diabetic check	66AD.00
Unclear	diabetic dietary review declined	8IAs.00

Code-type	Description	Read code
Unclear	referral to community diabetes specialist nurse decli	8IEQ.00
Unclear	diabetes mellitus with gangrene	C107.11
Unclear	malnutrit-related diabetes mellitus wth ophthalmic co	C10A300
Unclear	declined diabetic retinop scrn	9m0A.00
Unclear	diabetes monitor. check done	9OLA.00
Unclear	diabetes mellitus with other specified manifestation	C10y.00
Unclear	o/e - right eye background diabetic retinopathy	2BBP.00
Unclear	pt advised re diabetic diet	8CA4100
Unclear	diabetology d.v. done	8HLE.00
Unclear	diabetes screening administration	9Oy..00
Unclear	diabetic-uncooperative patient	66AL.00
Unclear	referral to diabetes special interest general practit	8H4e.00
Unclear	excluded from diabetic retinopathy screening as moved	9m05.00
Unclear	diabetes mellitus with peripheral circulatory disorde	C107.00
Unclear	neonatal diabetes mellitus	Q441.00
Unclear	exclu diab ret screen as blind	9m08.00
Unclear	diabetic erectile dysfunction review	66Au.00
Unclear	diabetes clinical pathway	8CMW700
Unclear	eligb perm inactv diab ret scr	9m03.00
Unclear	understands diet - diabetes	66A9.00
Unclear	o/e - left eye stable treated prolif diabetic retinop	2BBl.00
Unclear	diabetic annual review	66AS.00
Unclear	discharged from diabetes shared care programme	8HgC.00
Unclear	referral to diabetic eye clinic	8HTk.00
Unclear	asymptomatic diabetic neuropathy	F372200
Unclear	malnutrition-related diabetes mellitus wth neuro comp	C10A400
Unclear	acute painful diabetic neuropathy	F372000
Unclear	pre-existing diabetes mellitus, unspecified	L180X00
Unclear	hb. a1c - diabetic control	42W..00
Unclear	patient offered diabetes structured education program	679R.00
Unclear	[x] adverse reaction to insulins and antidiabetic age	U60231E
Unclear	malnutrition-related diabetes mellitus	C10A.00
Unclear	diabetic iritis	F440700
Unclear	non proliferative diabetic retinopathy	F420600
Unclear	high risk proliferative diabetic retinopathy	F420700
Unclear	[d]widespread diabetic foot gangrene	R054300
Unclear	seen in community diabetic specialist nurse clinic	9N0o.00
Unclear	diabetic weight reducing diet	13AC.00
Unclear	follow-up diabetic assessment	66A2.00
Unclear	o/e - no left diabetic retinopathy	2BBK.00
Unclear	impair vision due diab retinop	2BBr.00
Unclear	o/e - left eye diabetic maculopathy	2BBX.00
Unclear	nephrotic syndrome in diabetes mellitus	K01x100
Unclear	unstable diabetes	66AJ.11
Unclear	o/e - left diabetic foot - ulcerated	2G5L.00

Code-type	Description	Read code
Unclear	patient on maximal tolerated therapy for diabetes	8BL2.00
Unclear	seen by diabetic liaison nurse	9N2i.00
Unclear	diabetic mononeuropathy	F3y0.00
Unclear	o/e - right eye proliferative diabetic retinopathy	2BBT.00
Unclear	diabetes care by hospital only	66AU.00
Unclear	ischaemic ulcer diabetic foot	M271000
Unclear	o/e - right chronic diabetic foot ulcer	2G5V.00
Unclear	referral to community diabetes service	8Hlc.00
Unclear	neuropathic diabetic ulcer - foot	M271100
Unclear	diabetes care plan declined	8IE2.00
Unclear	[x]glomerular disorders in diabetes mellitus	Kyu0300
Unclear	background diabetic retinopathy	F420000
Unclear	diabetes management plan given	66AR.00
Unclear	annual diabetic blood test	66AT.00
Unclear	malnutrit-related diabetes mellitus with unspec compl	C10AW00
Unclear	preproliferative diabetic retinopathy	F420200
Unclear	did not attend diabetic retinopathy clinic	9N4p.00
Unclear	diabetes structured education programme declined	9OLM.00
Unclear	eligb temp inactv diab ret scr	9m02.00
Unclear	[x] adverse reaction to insulins and antidiabetic age	U602311
Unclear	polyneuropathy in diabetes	F372.00
Unclear	diabetes mellitus nos with ketoacidosis	C101z00
Unclear	diabetic assessment of erectile dysfunction	66Av.00
Unclear	advanced diabetic retinal disease	F420500
Unclear	excluded frm diabetic retinopathy screen as terminal	9m0C.00
Unclear	diabetic cheiroarthropathy	N030000
Unclear	hba1 - diabetic control	42c..00
Unclear	discharge by diabetic liaison nurse	ZLD7500
Unclear	diabetic 6 month review	66Ai.00
Unclear	excepted from diabetes qual indicators: patient unsui	9h41.00
Unclear	diabetes well being questionnaire	3882.00
Unclear	diabetic neuropathy	F372.12
Unclear	foot abnormality - diabetes related	2G5C.00
Unclear	diabetic peripheral angiopathy	G73y000
Unclear	diabetes clinical management plan	8CR2.00
Unclear	[x]diabetes mellitus	Cyu2.00
Unclear	retinal abnormality - diabetes related	2BBF.00
Unclear	diabetes treatment satisfaction questionnaire	3883.00
Unclear	diabetes mellitus nos with peripheral circulatory dis	C107z00
Unclear	dwbq - diabetes wellbeing questionnaire	ZRB6.11
Unclear	listed for diabetology admissn	8HME.00
Unclear	seen by diabetic liaison nurse	ZLA2500
Unclear	initial diabetic assessment	66A1.00
Unclear	pre-existing malnutrition-related diabetes mellitus	L180700
Unclear	referral to community diabetes clinic	8HTE100

Code-type	Description	Read code
Unclear	diabetic cataract	F464000
Unclear	[x]malnutrit-related diabetes mellitus with unspec co	Cyu2200
Unclear	o/e - right eye preproliferative diabetic retinopathy	2BBR.00
Unclear	did not complete diabetes structured education progra	8I81.00
Unclear	diabetic amyotrophy	F381311
Unclear	diabetes mellitus with nephropathy nos	C104z00
Unclear	refer, diabetic liaison nurse	8H7C.00
Unclear	maternally inherited diabetes mellitus	C10FS00
Unclear	discharged from care of diabetes specialist nurse	8Hg4.00
Unclear	diabetes structured education programme completed	9OLF.00
Unclear	diabetic foot risk assessment	66AW.00
Unclear	referral to dafne diabetes structured education progr	8Hj3.00
Unclear	seen in community diabetes specialist clinic	9N0n.00
Unclear	lipoatrophic diabetes mellitus without complication	C10M000
Unclear	transition of diabetes care options discussed	8CP2.00
Unclear	diabetic cheiropathy	N030011
Unclear	diabetic retinopathy screening refused	8I3X.00
Unclear	diabetic retinopathy 6 month review	8HBH.00
Unclear	o/e - left eye preproliferative diabetic retinopathy	2BBS.00
Unclear	referral to diabetologist	8H4F.00
Unclear	diabetes mellitus	C10..00
Unclear	other specified diabetes mellitus with neurological c	C106y00
Unclear	admit diabetic emergency	8H2J.00
Unclear	foot abnormality - diabetes related	2G51000
Unclear	o/e - right diabetic foot - ulcerated	2G5H.00
Unclear	referral to multidisciplinary diabetic clinic	8HTi.00
Unclear	diabetic - good control	66AI.00
Unclear	cellulitis in diabetic foot	M037200
Unclear	diabetes treatment satisfaction questionnaire	ZRB5.00
Unclear	date diabetic treatment stopp.	66AO.00
Unclear	diabetic retinopathy screening administrative status	9m0..00
Unclear	[d]gangrene of toe in diabetic	R054200
Unclear	xpert diabetes structured education programme complet	9OLL.00
Unclear	o/e - right diabetic foot at low risk	2G5E.00
Unclear	diabetic digital retinopathy screening offered	68AB.00
Unclear	diabetes monitor.verbal invite	9OL7.00
Unclear	diabetes mellitus with polyneuropathy	C106.13
Unclear	informed consent for diabetes national audit	9M00.00
Unclear	diabetic lipid lowering diet	13AB.00
Unclear	pre-conception advice for diabetes mellitus	67IJ100
Unclear	diabetes mellitus induced by non-steroid drugs	C10H.00
Unclear	diab mellit insulin-glucose infus acute myocardial in	889A.00
Unclear	attending diabetes clinic	9NM0.00
Unclear	referral to community diabetes specialist nurse	8Hl4.00
Unclear	advanced diabetic maculopathy	F420300

Code-type	Description	Read code
Unclear	other specified diabetes mellitus with other spec com	C10yy00
Unclear	injection sites - diabetic	66AA.11
Unclear	diabetes mellitus nos with unspecified complication	C10zz00
Unclear	diabetic - poor control	66AJ.00
Unclear	proliferative diabetic retinopathy	F420100
Unclear	ex diab ret scr no cntct detls	9m0B.00
Unclear	diabetic - follow-up default	66AM.00
Unclear	diabetes mellitus with ketoacidotic coma	C103.00
Unclear	diabetes mellitus nos with neurological manifestation	C106z00
Unclear	diabetic medicine	9b92000
Unclear	declined consent for diabetes year of care programme	66AQ100
Unclear	[x]unspecified diabetes mellitus with renal complicat	Cyu2300
Unclear	non-urgent diabetic admission	8H3O.00
Unclear	diabetes care plan agreed	8CS0.00
Unclear	o/e - no right diabetic retinopathy	2BBJ.00
Unclear	eligible for diabetic retinopathy screening	9m00.00
Unclear	malnutrit-relat diabetes mellitus with other spec com	C10AX00
Unclear	myasthenic syndrome due to diabetic amyotrophy	F381300
Unclear	seen in diabetic eye clinic	9N1v.00
Unclear	o/e - right diabetic foot at risk	2G5A.00
Unclear	seen in multidisciplinary diabetic clinic	9N1o.00
Unclear	conversion to insulin	66AH000
Unclear	diabetic retinopathy	F420.00
Unclear	[v]dietary counselling in diabetes mellitus	ZV65312
Unclear	diabetes mellitus with neuropathy	C106.12
Unclear	diabetic - cooperative patient	66AK.00
Unclear	diabetes mellitus with ophthalmic manifestation	C105.00
Unclear	diabetic peripheral neuropathy screening	66Ac.00
Unclear	diabetic foot examination not indicated	8I6G.00
Unclear	malnutrition-related diabetes mellitus with coma	C10A000
Unclear	diabetes medication review	8B3l.00
Unclear	diabetic on insulin and oral treatment	66AV.00
Unclear	other specified diabetes mellitus with renal complica	C104y00
Unclear	diabetic on subcutaneous treatment	66As.00
Unclear	diabetic maculopathy	F420400
Unclear	diabetic diet - good compliance	66AY.00
Unclear	refer to diabetic foot screener	8H7r.00
Unclear	other specified diabetes mellitus with coma	C103y00
Unclear	o/e - left diabetic foot at increased risk	2G5d.00
Unclear	date diabetic treatment start	66AN.00
Unclear	diabetes mellitus nos with hyperosmolar coma	C102z00
Unclear	diabetic stabilisation	8A13.00
Unclear	diabetic foot screen	66Aq.00
Unclear	under care of diabetologist	9NN8.00
Unclear	informed dissent for diabetes national audit	9M10.00

Code-type	Description	Read code
Unclear	adverse reaction to insulins and antidiabetic agents	TJ23.00
Unclear	diabetic retinopathy 12 month review	8HBG.00
Unclear	referral to diabetic liaison nurse	ZL62600
Unclear	malnutrition-related diabetes mellitus without compli	C10A700
Unclear	other specified diabetes mellitus with multiple comps	C108y00
Unclear	o/e - right diabetic foot at increased risk	2G5e.00
Unclear	other specified diabetes mellitus with unspecified co	C10zy00
Unclear	under care of diabetes specialist nurse	9NN9.00
Unclear	diabetic on insulin	66A5.00
Unclear	referral to diabetes nurse	8H7f.00
Unclear	did not complete dafne diabetes structured education	8I82.00
Unclear	patient consent given for addition to diabetic regist	93C4.00
Unclear	diabetes self-management plan review	661N400
Unclear	diabetic foot examination declined	8I3W.00
Unclear	unsuitable for diabetes year of care programme	66AQ000
Unclear	did not attend dafne diabetes structured education pr	9NiC.00
Unclear	diabetes clinic satisfaction questionnaire	ZRB4.00
Unclear	diabetic amyotrophy	C106.11
Unclear	referral to diabetes preconception counselling clinic	8HTe.00
Unclear	clinical diabetic nephropathy	K08yA11
Unclear	diabetes mellitus nos with ophthalmic manifestation	C105z00
Unclear	diabetes monitored	9OLA.11
Unclear	unspecified diabetes mellitus with multiple complicat	C108z00
Unclear	diabetic mononeuritis nos	F35z000
Unclear	[x]other specified diabetes mellitus	Cyu2000
Unclear	diabetes mellitus with hyperosmolar coma	C102.00
Unclear	o/e - right eye stable treated prolif diabetic retino	2BBk.00
Unclear	diabetes self-management plan agreed	661M400
Unclear	diabetic nephropathy	C104.11
Unclear	o/e - left diabetic foot at high risk	2G5K.00
Unclear	excepted from diabetes qual indicators: service unava	9h43.00
Unclear	diabetic - poor control nos	66AJz00
Unclear	dna - did not attend diabetic clinic	9N4I.00
Unclear	[x]malnutrit-relat diabetes mellitus with other spec	Cyu2100
Unclear	diabetes mellitus in pueperium - baby previously deli	L180400
Unclear	o/e - right diabetic foot at moderate risk	2G5F.00
Unclear	did not attend diabetes foot screening	9NiZ.00
Unclear	seen in diabetic clinic	9N1Q.00
Unclear	other specified diabetes mellitus with ketoacidosis	C101y00
Unclear	excluded from diabetic retinopathy screening	9m04.00
Unclear	malnutritn-relat diabetes melitus wth periph circul c	C10A500
Unclear	diabetes mellitus nos with other specified manifestat	C10yz00
Unclear	o/e - sight threatening diabetic retinopathy	2BBo.00
Unclear	seen by diabetologist	9N2d.00
Unclear	attended dafne diabetes structured education programm	9OLH.00

Code-type	Description	Read code
Unclear	diabetic patient unsuitable for digital retinal photo	9OLD.00
Unclear	[x]pre-existing diabetes mellitus, unspecified	Lyu2900
Unclear	diabetes mellitus with renal manifestation	C104.00
Unclear	high risk non proliferative diabetic retinopathy	F420800
Unclear	o/e - left diabetic foot at moderate risk	2G5J.00
Unclear	diabetic crisis monitoring	8A12.00
Unclear	diabetes mellitus nos with no mention of complication	C100z00
Unclear	diabetic retinopathy screening	68A7.00
Unclear	diabetes with gangrene	C107.12
Unclear	h/o: diabetes mellitus	1434.00
Unclear	provision of diabetes clinical summary	67D8.00
Unclear	exception reporting: diabetes quality indicators	9h4..00
Unclear	o/e - right diabetic foot at high risk	2G5G.00
Unclear	diabetology d.v. requested	8HKE.00
Unclear	patient diabetes education review	66Af.00
Unclear	proteinuric diabetic nephropathy	K08yA00
Unclear	patient held diabetic record declined	8I57.00
Unclear	dtsq - diabetes treatment satisfaction questionnaire	ZRB5.11
Unclear	o/e - right eye diabetic maculopathy	2BBW.00
Unclear	o/e - left chronic diabetic foot ulcer	2G5W.00
Unclear	did not attend diabetes structured education programm	9NiA.00
Unclear	diabetes: practice programme	66AP.00
Unclear	other specified diabetes mellitus with ophthalmic com	C105y00
Unclear	hb. a1c - diabetic control nos	42WZ.00
Unclear	malnutrition-related diabetes mellitus with renal com	C10A200
Unclear	high risk of diabetes mellitus annual review	66Az.00
Unclear	under care of diabetic liaison nurse	ZL22500
Unclear	diabetic retinopathy screening offered	68A9.00
Unclear	diabetic treatment changed	66AH.00
Unclear	diabetes mellitus nos with ketoacidotic coma	C103z00
Unclear	excluded from diabetic retinopthy screen as learn dis	9m0D.00
Unclear	diabetes: shared care programme	66AQ.00
Unclear	o/e - diabetic maculopathy absent both eyes	2BBM.00
Unclear	dafne diabetes structured education programme complet	9OLJ.00
Unclear	brittle diabetes	66AJ100
Unclear	diabetes mellitus with unspecified complication	C10z.00
Unclear	h/o: admission in last year for diabetes foot problem	14F4.00
Unclear	diabetic diet	13B1.00
Unclear	under care of diabetic foot screener	9NND.00
Unclear	diabetic drug side effects	66AG.00
Unclear	lipoatrophic diabetes mellitus	C10M.00
Unclear	excluded diabetc retinop screen as under care ophthal	9m07.00
Unclear	o/e - left eye proliferative diabetic retinopathy	2BBV.00
Unclear	seen in diabetic foot clinic	9N1i.00
Unclear	diabetes mellitus with no mention of complication	C100.00

Code-type	Description	Read code
Unclear	diabetic foot examination	66Ab.00
Unclear	education in self management of diabetes	679L000
Unclear	seen in diabetic nurse consultant clinic	9N0m.00
Unclear	ineligible for diabetic retinopathy screening	9m01.00
Unclear	adverse reaction to insulins and antidiabetic agents	TJ23z00
Unclear	malnutrition-related diabetes mellitus with ketoacido	C10A100

Supplementary Table 4A2 Drug Code List used to identify individuals with diabetes mellitus

Diabetes Drug Class	Description	drugcode
Short-acting insulin	INSULIN GLULISIN 100iu/mL cart	86549998
Short-acting insulin	INSULIN GLULISINE 100iu/mL vls	86551998
Short-acting insulin	Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges	96049998
Short-acting insulin	INSULIN ASPART 100u/mL cart	60064979
Short-acting insulin	Insulin soluble bovine 100unit/ml Injection	98474990
Short-acting insulin	Insulin human 1mg inhalation powder blisters	86047998
Short-acting insulin	Insulin human 3mg inhalation powder blisters	86046998
Short-acting insulin	Insulin soluble human 100units/ml solution for injection 10ml vials	86319998
Short-acting insulin	INSULIN LISPRO 100iu/mL pen	83403998
Short-acting insulin	Human insulin 100u/mL inj cart	86174998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	88999998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL carts	86314998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	86312998
Short-acting insulin	INSULIN ASPART 100u/mL syrnge	91612998
Short-acting insulin	INSULIN HUMULIN S (NEUTRAL) CARTRIDGE 100 I/U	96787992
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	86316998
Short-acting insulin	Insulin neutral human 100unit/ml Injection	96048998
Short-acting insulin	Insulin soluble porcine 100units/ml solution for injection 10ml vials	86185998
Short-acting insulin	Insulin soluble human pyr 100unit/ml Injection	90691998
Short-acting insulin	Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges	98480998
Short-acting insulin	INSULIN ASPART 100units/mL pen	81164998
Short-acting insulin	Human Insulin 100u/mL inj pen	86313998
Short-acting insulin	INSULIN NEUSULIN (NEUTRAL)(PURIFIED) 100 I/U INJ	94202992
Short-acting insulin	Insulin glulisine 100unit/ml Solution for injection	86553998
Short-acting insulin	Insulin aspart human pyr 100 iu/ml Injection	90379998
Short-acting insulin	Insulin neutral human 100unit/ml Injection	96047998
Short-acting insulin	INSULIN GLULISINE 100iu/mL pen	86215998
Short-acting insulin	Insulin glulisine 100units/ml solution for injection 10ml vials	86237998
Short-acting insulin	INSULIN SOLUBLE 40 I/U INJ	97602992
Short-acting insulin	INSULIN ASPART 100u/mL cart	98198998
Short-acting insulin	Insulin soluble human emp 100unit/ml Injection	90690998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	96286992
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	95162992
Short-acting insulin	INSULIN SOLUBLE INJ I/U^2	93467992
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	99557998
Short-acting insulin	HUMAN INSULIN 3mg pdr for inh	86044998
Short-acting insulin	Human Insulin 100u/mL inj pen	97322997
Short-acting insulin	INSULIN SOLUBLE 100 I/U INJ	99976992
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	88413998
Short-acting insulin	Insulin lispro 100units/ml solution for injection 3ml cartridges	86255998
Short-acting insulin	Human Insulin 100u/mL inj pen	91274998
Short-acting insulin	HUMAN INSULIN 1mg pdr for inh	86045998
Short-acting insulin	INSULIN NEUTRAL (HUMAN) 100 I/U INJ	96688992

Diabetes Drug Class	Description	drugcode
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	98227998
Short-acting insulin	INSULIN ASPART 100units/mL pen	87435979
Short-acting insulin	INSULIN LISPRO 100iu/mL pen	86251998
Short-acting insulin	INSULIN ASPART 100units/mL pen	91509998
Short-acting insulin	Insulin soluble porcine 100units/ml solution for injection 3ml cartridges	86184998
Short-acting insulin	Insulin glulisine 100units/ml solution for injection 3ml pre-filled disposable devices	86214998
Short-acting insulin	INSULIN ASPART 100units/mL pen	87434979
Short-acting insulin	Insulin aspart 100units/ml solution for injection 3ml pre-filled disposable devices	86263998
Short-acting insulin	Insulin soluble human 100units/ml solution for injection 3ml cartridges	86315998
Short-acting insulin	Insulin soluble human crb 100iu/ml Injection	88003998
Short-acting insulin	Insulin soluble bovine 100units/ml solution for injection 10ml vials	86176998
Short-acting insulin	INSULIN ASPART 100u/mL vial	99402998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	95158992
Short-acting insulin	Insulin soluble human emp 100unit/ml Injection	94292998
Short-acting insulin	INSULIN QUICKSOL (SOLUBLE NEUTRAL) 100 I/U INJ	96295992
Short-acting insulin	Insulin lispro 100units/ml solution for injection 1.5ml cartridges	90012998
Short-acting insulin	INSULIN LISPRO 100iu/mL pen	93572979
Short-acting insulin	INSULIN NEUTRAL (PURIFIED) 100 I/U INJ	96290992
Short-acting insulin	INSULIN LISPRO 100iu/mL carts	86252998
Short-acting insulin	Insulin soluble human prb 100unit/ml Injection	90689998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	94477992
Short-acting insulin	Insulin soluble porcine 100units/ml solution for injection 1.5ml cartridges	94948998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL carts	97322998
Short-acting insulin	Human Insulin 100u/mL inj pen	90202979
Short-acting insulin	Human insulin 100u/mL inj cart	96065998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	86183998
Short-acting insulin	INSULIN ASPART 100u/mL cart	87442979
Short-acting insulin	INSULIN LISPRO 100iu/mL vials	86253998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL carts	86182998
Short-acting insulin	INSULIN BP 100 I/U	96044992
Short-acting insulin	Insulin soluble human 100units/ml solution for injection 3ml cartridges	86317998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	99553998
Short-acting insulin	Neutral insulin bovine 100unit/ml Injection	96050998
Short-acting insulin	INSULIN LISPRO 100iu/mL pen	90015998
Short-acting insulin	Insulin soluble bovine cartridge 100unit/ml Solution for injection	86175998
Short-acting insulin	Human insulin 100u/mL inj cart	97525998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	98982998
Short-acting insulin	Insulin lispro 100units/ml solution for injection 3ml pre-filled disposable devices	86254998
Short-acting insulin	Insulin lispro 100units/ml solution for injection 10ml vials	86256998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL carts	88851998
Short-acting insulin	Insulin glulisine 100units/ml solution for injection 3ml cartridges	86236998
Short-acting insulin	NEUTRAL INSULIN 100iu/mL 10mL	86173998
Short-acting insulin	Insulin glulisine 100units/ml solution for injection 3ml cartridges	85591998
Short-acting insulin	Insulin aspart 100units/ml solution for injection 10ml vials	86265998
Short-acting insulin	INSULIN GLULISINE 100iu/mL pen	84421998
Short-acting insulin	Insulin aspart 100units/ml solution for injection 3ml cartridges	86264998

Diabetes Drug Class	Description	drugcode
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges	86169998
Intermediate\Long-acting insulin	Insulin zinc mixed human 100units/ml suspension for injection 10ml vials	90685998
Intermediate\Long-acting insulin	Insulin isophane porcine 100units/ml suspension for injection 1.5ml cartridges	96055998
Intermediate\Long-acting insulin	Isoph insulin hum 100u/mL pen	86266998
Intermediate\Long-acting insulin	Insulin biphasic isophane human crb 25:75; 100 units/ml Injection	92376997
Intermediate\Long-acting insulin	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices	86249998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 30:70; 100 units/ml Injection	90684996
Intermediate\Long-acting insulin	Insulin isophane human crb 100iu/ml Injection	94322998
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 1.5ml cartridges	98228997
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 30:70; 100 units/ml Injection	97052996
Intermediate\Long-acting insulin	INSULIN HUMULIN M4 CARTRIDGE 100 I/U	96046992
Intermediate\Long-acting insulin	INSULIN HYPURIN PROTAMINE ZINC 100 I/U INJ	96285992
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	96291992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges	86309998
Intermediate\Long-acting insulin	Insulin glargine 100units/ml solution for injection 3ml cartridges	86241998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml pre-filled disposable devices	91294997
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 5ml vials	91700998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices	91292997
Intermediate\Long-acting insulin	Insulin zinc suspension crystalline human pyr 100unit/ml long acting Injection	96058998
Intermediate\Long-acting insulin	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices	86077998
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 5ml vials	86267998
Intermediate\Long-acting insulin	Insulin isophane human prb 100iu/ml Injection	90687998
Intermediate\Long-acting insulin	Insulin isophane porcine 100units/ml suspension for injection 3ml cartridges	86193998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	86191998
Intermediate\Long-acting insulin	Isoph insulin hum 100u/mL pen	81426998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices	81963998
Intermediate\Long-acting insulin	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials	86189998
Intermediate\Long-acting insulin	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges	86188998
Intermediate\Long-acting insulin	INSULIN DETEMIR 100iu/mL syrg	84779998
Intermediate\Long-acting insulin	Insulin biphasic lispro human prb 25:75; 100 units/ml Injection	89990998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges	86306998
Intermediate\Long-acting insulin	INSULIN ISOPHANE (HIGHLY PURIFIED) 100 I/U INJ	96292992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 5ml vials	92376996
Intermediate\Long-acting insulin	Insulin biphasic isophane human emp 30:70; 100 units/ml Injection	89888998
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 40:60; 100 units/ml Injection	97051998
Intermediate\Long-acting insulin	Insulin biphasic lispro human prb 50:50; 100 units/ml Injection	89990997
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices	90169998
Intermediate\Long-acting insulin	INSULIN ISOPHANE 50%/NEUTRAL 50% 100 I/U INJ	99977992

Diabetes Drug Class	Description	drugcode
Intermediate\Long-acting insulin	HUMAN ISOPH INS 100u/mL cart	86268998
Intermediate\Long-acting insulin	Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials	82457998
Intermediate\Long-acting insulin	Insulin zinc suspension mixed human pyr 100unit/ml Injection	96060998
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 3ml cartridges	86275998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml pre-filled disposable devices	91291997
Intermediate\Long-acting insulin	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges	86028998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials	86280998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials	86078998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 5ml vials	86283998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml pre-filled disposable devices	86284998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges	86294998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges	86291998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 40/60 100units/ml suspension for injection 3ml cartridges	86295998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 30:70; 100 units/ml Injection	91292996
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices	86298998
Intermediate\Long-acting insulin	INSULIN GLARGINE 100iu/mL vial	86240998
Intermediate\Long-acting insulin	INSULIN ISOPHANE (PURIFIED) 100 I/U INJ	99978992
Intermediate\Long-acting insulin	INSULIN GLARGINE 100iu/mL pen	84422998
Intermediate\Long-acting insulin	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices	92323998
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 40:60; 100 units/ml Injection	91273998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	97599992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials	86305998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 10ml vials	91290996
Intermediate\Long-acting insulin	INSULN ZINC LENTE 100iu/mL in	97527998
Intermediate\Long-acting insulin	Isoph insulin hum 100u/mL pen	91295998
Intermediate\Long-acting insulin	Biphas aspart 30/70 pen 3mL	86259998
Intermediate\Long-acting insulin	INSULIN GLARGINE 100iu/mL cart	89668979
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 10:90; 100 units/ml Injection	97052998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	99533998
Intermediate\Long-acting insulin	Biphas aspart 30/70 pen 3mL	89554998
Intermediate\Long-acting insulin	Biphasic aspart 30/70 cart 3m	86260998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices	86304998
Intermediate\Long-acting insulin	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 3ml cartridges	86186998
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices	91505998
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 25:75; 100 units/ml Injection	87967998
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 20:80; 100 units/ml Injection	91275997
Intermediate\Long-acting insulin	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml cartridges	86029998
Intermediate\Long-acting insulin	INSULN ZINC LENTE 100iu/mL in	97053998

Diabetes Drug Class	Description	drugcode
Intermediate\Long-acting insulin	Insulin biphasic isophane human emp 50:50; 100 units/ml Injection	98225998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	95163992
Intermediate\Long-acting insulin	Insulin isophane human vial 100unit/ml Sterile suspension injection	86276998
Intermediate\Long-acting insulin	Insulin detemir 100units/ml solution for injection 3ml cartridges	86246998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 1.5ml cartridges	87416979
Intermediate\Long-acting insulin	INSULIN PUR-IN MIX 15/85 100 I/U INJ	96794992
Intermediate\Long-acting insulin	Insulin glargine 100units/ml solution for injection 3ml pre-filled disposable devices	86242998
Intermediate\Long-acting insulin	Insulin biphasic isophane human emp 25:75; 100 units/ml Injection	94298998
Intermediate\Long-acting insulin	INSULIN ISOPHANE (HUMAN) 100 I/U INJ	93137992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices	86288998
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 20:80; 100 units/ml Injection	90697997
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	99532998
Intermediate\Long-acting insulin	Insulin biphasic isophane human emp 30:70; 100 units/ml Injection	98226998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges	86279998
Intermediate\Long-acting insulin	Insulin glargine 100units/ml solution for injection 10ml vials	86243998
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices	86274998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 30:70; 100 units/ml Injection	91292998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges	86308998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL cart	86177998
Intermediate\Long-acting insulin	HUMAN ISOPH INS 100u/mL cart	86190998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices	81790998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml pre-filled disposable devices	91293997
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 10ml vials	97051997
Intermediate\Long-acting insulin	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices	86261998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL cart	86270998
Intermediate\Long-acting insulin	Insulin zinc suspension mixed bovine and porcine 100unit/ml Injection	90698998
Intermediate\Long-acting insulin	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges	86248998
Intermediate\Long-acting insulin	INSULIN BOVINE PROTAMINE ZINC 40 I/U INJ	97600992
Intermediate\Long-acting insulin	HUMAN ISOPH INS 100u/mL cart	88995998
Intermediate\Long-acting insulin	INSULIN ISOPHANE 100 I/U	93139992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges	90683997
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 40:60; 100 units/ml Injection	92907998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 20:80; 100 units/ml Injection	94328998
Intermediate\Long-acting insulin	Isoph insulin hum 100u/mL pen	98228998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml cartridges	86282998
Intermediate\Long-acting insulin	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices	83405998
Intermediate\Long-acting insulin	Insulin aspart biphasic 30/70 100units/ml suspension for injection 3ml cartridges	86262998
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 10:90; 100 units/ml Injection	91275998

Diabetes Drug Class	Description	drugcode
Intermediate\Long-acting insulin	Isoph insulin hum 100u/mL pen	97854998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 30:70; 100 units/ml Injection	94337998
Intermediate\Long-acting insulin	Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials	96057998
Intermediate\Long-acting insulin	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 1.5ml cartridges	88978998
Intermediate\Long-acting insulin	INSULIN GLARGINE 100iu/mL pen	89640979
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL cart	97526998
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 50:50; 100 units/ml Injection	91273997
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 40:60; 100 units/ml Injection	90682998
Intermediate\Long-acting insulin	INSULIN SEMITARD 40 I/U INJ	95168992
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 40:60; 100 units/ml Injection	91291998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	96056998
Intermediate\Long-acting insulin	Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials	97528998
Intermediate\Long-acting insulin	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 1.5ml cartridges	96053997
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 10:90; 100 units/ml Injection	90697998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 30:70; 100 units/ml Injection	92932998
Intermediate\Long-acting insulin	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials	86187998
Intermediate\Long-acting insulin	INSULIN GLARGINE 100iu/mL cart	86238998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices	86278998
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 50:50; 100 units/ml Injection	90682997
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 1.5ml cartridges	87411979
Intermediate\Long-acting insulin	Isophane insulin 100iu/ml Injection	96045998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 40:60; 100 units/ml Injection	90683998
Intermediate\Long-acting insulin	INSULIN HUMULIN M4 100 I/U INJ	96284992
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 10:90; 100 units/ml Injection	91294998
Intermediate\Long-acting insulin	INSULIN DETEMIR 100iu/mL carts	87472998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 20/80 100units/ml suspension for injection 3ml cartridges	97052997
Intermediate\Long-acting insulin	Insulin lispro biphasic 25/75 100units/ml suspension for injection 10ml vials	82458998
Intermediate\Long-acting insulin	Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials	96046998
Intermediate\Long-acting insulin	INSULIN DETEMIR 100iu/mL pen	87471998
Intermediate\Long-acting insulin	INSULIN SEMITARD 100 I/U INJ	96064992
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 10:90; 100 units/ml Injection	90684998
Intermediate\Long-acting insulin	HUMAN ISOPH INS 100u/mL syrng	86080998
Intermediate\Long-acting insulin	INSULIN HUMULIN M CARTRIDGE 100 I/U	96548992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges	86311998
Intermediate\Long-acting insulin	Insulin zinc suspension amorphous porcine 100unit/ml Injection	99144998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 10:90; 100 units/ml Injection	94319998
Intermediate\Long-acting insulin	Insulin isophane human prb 100iu/ml Injection	99554998
Intermediate\Long-acting insulin	Insulin isophane bovine 100units/ml suspension for injection 1.5ml cartridges	98048990

Diabetes Drug Class	Description	drugcode
Intermediate\Long-acting insulin	Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials	98817998
Intermediate\Long-acting insulin	INSULIN DEPO S.C.S. 5 400 I/U INJ	97244992
Intermediate\Long-acting insulin	Insulin biphasic isophane human prb 30:70; 100 units/ml Injection	90697996
Intermediate\Long-acting insulin	HUMAN ISOPH INS 100u/mL syrng	90168998
Intermediate\Long-acting insulin	Insulin soluble human 100units/ml solution for injection 3ml pre-filled disposable devices	86318998
Intermediate\Long-acting insulin	Insulin lispro biphasic 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices	87365979
Intermediate\Long-acting insulin	INSULIN ISOPHANE (NPH) 100 I/U INJ	96283992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges	86303998
Intermediate\Long-acting insulin	Insulin glargine 100iu/ml Injection	91758998
Intermediate\Long-acting insulin	INSULIN ZINC CRYSTALLINE susp 100 I/U INJ	96689992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 15/85 100units/ml suspension for injection 5ml vials	91289998
Intermediate\Long-acting insulin	HUMAN ISOPH INS 100u/mL cart	98481997
Intermediate\Long-acting insulin	INSULIN GLARGINE 100iu/mL vial	92555998
Intermediate\Long-acting insulin	Insulin biphasic aspart human pyr 30:70; 100 units/ml Injection	89555998
Intermediate\Long-acting insulin	HUMAN ISOPH INS 100u/mL cart	98228996
Intermediate\Long-acting insulin	Insulin biphasic isophane human crb 25:75; 100 units/ml Injection	91701998
Intermediate\Long-acting insulin	INSULIN PUR-IN MIX 50/50 100 I/U INJ	96792992
Intermediate\Long-acting insulin	Insulin isophane human emp 100unit/ml Injection	90686998
Intermediate\Long-acting insulin	INSULIN ZINC BOVINE susp 100 I/U INJ	96294992
Intermediate\Long-acting insulin	INSULN ZINC LENTE 100iu/mL in	95846992
Intermediate\Long-acting insulin	Insulin isophane bovine 100units/ml suspension for injection 3ml cartridges	86179998
Intermediate\Long-acting insulin	Isoph insulin hum 100u/mL pen	91276998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	86271998
Intermediate\Long-acting insulin	Insulin zinc mixed bovine vial 100unit/ml Sterile suspension injection	96061998
Intermediate\Long-acting insulin	Insulin isophane biphasic porcine 30/70 100units/ml suspension for injection 10ml vials	99415998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges	94436998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	86178998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges	92906998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 40:60; 100 units/ml Injection	94413998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	97323998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml cartridges	86287998
Intermediate\Long-acting insulin	INSULIN NOVO ULTRATARD MC 100 I/U INJ	96289992
Intermediate\Long-acting insulin	INSULIN PUR-IN ISOPHANE 100 I/U INJ	96795992
Intermediate\Long-acting insulin	INSULIN GLARGINE 100iu/mL pen	86239998
Intermediate\Long-acting insulin	Insulin detemir 100 iu/ml Solution for injection	87473998
Intermediate\Long-acting insulin	INSULN ZINC LENTE 100iu/mL in	99401998
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices	81962998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 10:90; 100 units/ml Injection	92909998

Diabetes Drug Class	Description	drugcode
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 10ml vials	87385979
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 10ml vials	86300998
Intermediate\Long-acting insulin	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices	87373979
Intermediate\Long-acting insulin	INSULN ZINC LENTE 100iu/mL in	99556998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml pre-filled disposable devices	91275996
Intermediate\Long-acting insulin	INSULIN BOVINE PROTAMINE ZINC 100 I/U INJ	96076992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 15/85 100units/ml suspension for injection 3ml cartridges	81687998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	96282992
Intermediate\Long-acting insulin	INSULIN GLARGINE 100iu/mL cart	86272998
Intermediate\Long-acting insulin	Insulin biphasic 100 units/ml Injection	99196998
Intermediate\Long-acting insulin	Insulin protamine zinc bovine 100units/ml suspension for injection 10ml vials	96051998
Intermediate\Long-acting insulin	INSULN ZINC LENTE 100iu/mL in	95164992
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 20:80; 100 units/ml Injection	91293998
Intermediate\Long-acting insulin	Insulin zinc crystalline human 100units/ml suspension for injection 10ml vials	98268998
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 1.5ml cartridges	90688998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 30/70 100units/ml suspension for injection 3ml cartridges	86301998
Intermediate\Long-acting insulin	HUMAN ISOPH INS 100u/mL cart	86168998
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 20:80; 100 units/ml Injection	92908998
Intermediate\Long-acting insulin	INSULN ZINC LENTE 100iu/mL in	98505998
Intermediate\Long-acting insulin	Insulin zinc mixed bovine 100units/ml suspension for injection 10ml vials	98525990
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 1.5ml cartridges	91290998
Intermediate\Long-acting insulin	Insulin isophane bovine 100units/ml suspension for injection 10ml vials	86180998
Intermediate\Long-acting insulin	Insulin biphasic lispro human prb 25:75; 100 units/ml Injection	98895998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	98481998
Intermediate\Long-acting insulin	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices	86247998
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 10ml vials	86081998
Intermediate\Long-acting insulin	Insulin biphasic 100 units/ml Injection	96062998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices	91290997
Intermediate\Long-acting insulin	INSULN ZINC LENTE 100iu/mL in	99480998
Intermediate\Long-acting insulin	ISOPHANE INSULIN 100iu/mL 10m	96287992
Intermediate\Long-acting insulin	Insulin biphasic isophane human pyr 20:80; 100 units/ml Injection	90684997
Intermediate\Long-acting insulin	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml cartridges	86250998
Intermediate\Long-acting insulin	Insulin isophane biphasic human 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices	86281998
Intermediate\Long-acting insulin	Insulin lispro biphasic 25/75 100units/ml suspension for injection 3ml pre-filled disposable devices	83404998
Intermediate\Long-acting insulin	Insulin isophane human 100units/ml suspension for injection 3ml pre-filled disposable devices	86269998
Intermediate\Long-acting insulin	Insulin detemir 100units/ml solution for injection 3ml pre-filled disposable devices	86245998
Intermediate\Long-acting insulin	INSULN ZINC LENTE 100iu/mL in	94201992
Intermediate\Long-acting insulin	Insulin isophane biphasic human 10/90 100units/ml suspension for injection 3ml cartridges	86310998

Diabetes Drug Class	Description	drugcode
Intermediate\Long-acting insulin	Insulin isophane biphasic human 50/50 100units/ml suspension for injection 3ml pre-filled disposable devices	86286998
Intermediate\Long-acting insulin	Insulin isophane porcine 100units/ml suspension for injection 10ml vials	86194998
Sulphonylureas	GLIBORNURIDE 25mg tablets	99588998
Sulphonylureas	TOLBUTAMIDE 250 MG TAB	95674992
Sulphonylureas	GLIPIZIDE 2.5mg tablets	96281998
Sulphonylureas	GLIBENCLAMIDE 2.5mg tablets	99145998
Sulphonylureas	GLICLAZIDE 30mg m/r tablets	83916998
Sulphonylureas	GLIBENCLAMIDE 5mg tablets	99787998
Sulphonylureas	Gliquidone 30mg tablets	96280998
Sulphonylureas	GLIBENCLAMIDE 5mg tablets	97537997
Sulphonylureas	Glibenclamide 5mg tablets	99582990
Sulphonylureas	GLIBENCLAMIDE 5mg tablets	97583997
Sulphonylureas	ACETOHEXAMIDE 500mg tablets	99754998
Sulphonylureas	Tolbutamide 500mg tablets	99347990
Sulphonylureas	TOLBUTAMIDE 500mg tablets	97089998
Sulphonylureas	Chlorpropamide 100mg tablets	99246990
Sulphonylureas	TOLBUTAMIDE 100 MG TAB	94371992
Sulphonylureas	Glimepiride 1mg tablets	88449997
Sulphonylureas	Gliclazide 40mg/5ml oral suspension	86018998
Sulphonylureas	Glibenclamide 5mg tablets	97127997
Sulphonylureas	Gliclazide 80mg tablets	97032990
Sulphonylureas	Acetohexamide 500mg tablets	96981998
Sulphonylureas	GLIMEPIRIDE 3mg tablets	88447996
Sulphonylureas	GLICLAZIDE 30mg m/r tablets	83949998
Sulphonylureas	TOLAZAMIDE 100mg tablets	95149998
Sulphonylureas	Tolazamide 100mg Tablet	95150998
Sulphonylureas	Tolbutamide 500mg tablets	98053990
Sulphonylureas	GLIBENCLAMIDE 2.5mg tablets	99668998
Sulphonylureas	CHLORPROPAMIDE 500 MG TAB	97133992
Sulphonylureas	GLIMEPIRIDE 1mg tablets	88447997
Sulphonylureas	Glipizide 2.5mg tablets	96282998
Sulphonylureas	Tolbutamide 500mg tablets	97109998
Sulphonylureas	Glipizide 5mg tablets	96893990
Sulphonylureas	GLIMEPIRIDE 2mg tablets	88447998
Sulphonylureas	Gliclazide 80mg tablets	96283998
Sulphonylureas	Glimepiride 3mg tablets	88449996
Sulphonylureas	Glipizide 5mg tablets	97202990
Sulphonylureas	Gliclazide 80mg tablets	97938990
Sulphonylureas	Gliclazide 30mg modified-release tablets	82304998
Sulphonylureas	GLICLAZIDE 30mg m/r tablets	91407998
Sulphonylureas	Glibenclamide 5mg tablets	98664990
Sulphonylureas	GLIBENCLAMIDE 5mg tablets	99668997
Sulphonylureas	Gliclazide 40mg tablets	82137998
Sulphonylureas	Gliclazide 80mg tablets	96427990
Sulphonylureas	Glibenclamide 5mg/5ml oral suspension	85901998
Sulphonylureas	BUTAMIDE CAP	95870992

Diabetes Drug Class	Description	drugcode
Sulphonylureas	Tolazamide 250mg Tablet	95150997
Sulphonylureas	GLIBENCLAMIDE 2.5mg tablets	97583998
Sulphonylureas	DAONIL 10 MG TAB	97236992
Sulphonylureas	Chlorpropamide 250mg tablets	96755997
Sulphonylureas	Gliclazide 80mg tablets	97889990
Sulphonylureas	Gliclazide 80mg tablets	97026990
Sulphonylureas	GLIBENCLAMIDE 2.5mg tablets	97537998
Sulphonylureas	Tolbutamide 500mg tablets	99349990
Sulphonylureas	Glimepiride 2mg tablets	88449998
Sulphonylureas	GLICLAZIDE 40mg tablets	82136998
Sulphonylureas	Gliclazide 30mg modified-release tablets	82989998
Sulphonylureas	Glipizide 5mg tablets	96282997
Sulphonylureas	Gliclazide 80mg tablets	96495990
Sulphonylureas	Gliclazide 80mg tablets	97166990
Sulphonylureas	Glipizide 5mg tablets	97834990
Sulphonylureas	Gliclazide 30mg modified-release tablets	92831990
Sulphonylureas	GLIBENCLAMIDE 2.5mg tablets	97057997
Sulphonylureas	Gliclazide 80mg tablets	97538990
Sulphonylureas	Glibenclamide 5mg tablets	96220990
Sulphonylureas	Gliclazide 30mg modified-release tablets	96283997
Sulphonylureas	CHLORPROPAMIDE 100mg tablets	99764998
Sulphonylureas	Chlorpropamide 250mg tablets	98188989
Sulphonylureas	Gliclazide 80mg/5ml oral suspension	81260998
Sulphonylureas	Glibornuride 25mg Tablet	91559998
Sulphonylureas	GLICLAZIDE 80mg tablets	97303998
Sulphonylureas	Glibenclamide 2.5mg tablets	97127998
Sulphonylureas	GLIPIZIDE 5mg tablets	99591998
Sulphonylureas	Gliclazide 80mg tablets	98133990
Sulphonylureas	GLIQUIDONE 30mg tablets	99589998
Sulphonylureas	CHLORPROPAMIDE 250mg tablets	96687998
Sulphonylureas	CHLORPROPAMIDE 250mg tablets	99764997
Sulphonylureas	Chlorpropamide 100mg tablets	96755998
Sulphonylureas	TOLAZAMIDE 250mg tablets	95149997
Sulphonylureas	Glibenclamide 5mg tablets	99580990
Sulphonylureas	GLIBENCLAMIDE 5mg tablets	97097997
Sulphonylureas	Glibenclamide 2.5mg tablets	99580989
Sulphonylureas	GLIBENCLAMIDE 5mg tablets	97057998
Sulphonylureas	Glibenclamide 2.5mg tablets	99582989
Sulphonylureas	Glibenclamide 2.5mg tablets	97552990
Sulphonylureas	Gliclazide 80mg tablets	95898990
Sulphonylureas	Gliclazide 80mg tablets	97590990
Sulphonylureas	GLIPIZIDE 5mg tablets	99419998
Sulphonylureas	Gliclazide 80mg tablets	93545979
Sulphonylureas	Glibenclamide 2.5mg tablets	98664989
Sulphonylureas	GLIMEPIRIDE 4mg tablets	88334998
Sulphonylureas	Gliclazide 80mg tablets	95025990
Sulphonylureas	Glimepiride 4mg tablets	88355998

Diabetes Drug Class	Description	drugcode
Sulphonylureas	GLICLAZIDE 80mg tablets	88135998
Sulphonylureas	Glipizide 5mg tablets	97146990
Sulphonylureas	TOLBUTAMIDE 1 GM TAB	95672992
Sulphonylureas	TOLBUTAMIDE 500mg tablets	99195998
Metformin	Metformin 850mg tablets	99514989
Metformin	METFORMIN HCL 500mg/sachet pdr	82917998
Metformin	METFORMIN HCL 500mg tablets	91221998
Metformin	Metformin Oral solution	85555998
Metformin	Metformin 500mg modified-release tablets	89870979
Metformin	METFORMIN HCL 1000mg m/r tabs	89129979
Metformin	Metformin 1g oral powder sachets sugar free	82918998
Metformin	METFORMIN HCL 1000mg m/r tabs	83031998
Metformin	METFORMIN HCL 1000mg/sachet	82916998
Metformin	METFORMIN HCL 750mg m/r tabs	83732998
Metformin	Metformin 500mg tablets	97110990
Metformin	Metformin 500mg tablets	94248990
Metformin	Metformin 100mg/ml Oral solution	87536998
Metformin	Metformin 750mg modified-release tablets	83733998
Metformin	Metformin 500mg modified-release tablets	87054998
Metformin	METFORMIN 250 MG TAB	95272992
Metformin	METFORMIN HCL 500mg tablets	99590998
Metformin	METFORMIN HCL 500mg m/r tabs	81158998
Metformin	METFORMIN HCL 500mg m/r tabs	89868979
Metformin	Metformin 500mg oral powder sachets sugar free	82919998
Metformin	METFORMIN HCL 500mg m/r tabs	87053998
Metformin	Metformin 500mg/5ml oral solution sugar free	85673998
Metformin	METFORMIN HCL 500mg tablets	95880998
Metformin	Metformin 500mg tablets	95600990
Metformin	METFORMIN HCL 500mg tablets	81701998
Metformin	METFORMIN 800 MG TAB	95270992
Metformin	Metformin 850mg tablets	98493990
Metformin	Metformin 500mg tablets	98654989
Metformin	Metformin 500mg tablets	98493989
Metformin	Metformin 500mg/5ml oral solution sugar free	93167990
Metformin	Metformin 500mg/5ml oral solution sugar free	85674998
Metformin	Metformin 850mg tablets	97087997
Metformin	Metformin 500mg tablets	96111990
Metformin	Metformin 1g modified-release tablets	83032998
Metformin	METFORMIN HCL 1000mg m/r tabs	81344998
Metformin	Metformin 500mg tablets	99514990
Metformin	Metformin 500mg tablets	97087998
Metformin	METFORMIN HCl 500 MG TAB	94235992
Metformin	Metformin 850mg tablets	98654990
Metformin	Metformin 850mg/5ml oral solution	79510979
Metformin	METFORMIN HCL 500mg tablets	87883998
Metformin	METFORMIN HCL 850mg tablets	91221997
Metformin	METFORMIN HCL 500mg tablets	54786979

Diabetes Drug Class	Description	drugcode
Metformin	Metformin 500mg tablets	96270990
Metformin	Metformin 850mg tablets	98125989
Metformin	METFORMIN HCL 500mg m/r tabs	83619998
Metformin	Metformin 850mg tablets	99513989
Metformin	METFORMIN HCL 850mg tablets	99590997
Metformin	Metformin 500mg tablets	96850990
Metformin	Metformin 850mg tablets	97110989
Metformin	Metformin 500mg/5ml oral solution sugar free	92983990
Metformin	Metformin 500mg tablets	99149990
Metformin	Metformin 500mg tablets	99513990
Metformin	Metformin 500mg tablets	98125990
Metformin	METFORMIN HCl 850 MG TAB	95271992
Metformin	METFORMIN HCL 500mg m/r tabs	58558979
Acarbose	ACARBOSE 50mg tablets	98475998
Acarbose	Acarbose 50mg tablets	98915998
Acarbose	Acarbose 100mg tablets	98915997
Acarbose	ACARBOSE 100mg tablets	98475997
GLP-1	Exenatide 5micrograms/0.02ml solution for injection 1.2ml pre-filled disposable devices	84697998
GLP-1	LIRAGLUTIDE 6mg/mL pen	82793998
GLP-1	Exenatide 10micrograms/0.04ml solution for injection 2.4ml pre-filled disposable devices	84696998
GLP-1	EXENATIDE 5mcg/0.02mL inj pen	84694998
GLP-1	Liraglutide 6mg/ml solution for injection 3ml pre-filled disposable devices	82794998
GLP-1	Exenatide 2mg powder and solvent for suspension for injection vials	81307998
GLP-1	EXENATIDE 10mcg/0.04mL inj pen	84693998
GLP-1	EXENATIDE 2mg pdr+solv inj	81305998
Gliptins	LINAGLIPTIN 5mg tablets	81159998
Gliptins	Saxagliptin 2.5mg tablets	81514998
Gliptins	SITAGLIPTIN 100mg tablets	84639998
Gliptins	SAXAGLIPTIN 5mg tablets	82573998
Gliptins	SITAGLIPTIN 50mg tablets	59371979
Gliptins	Saxagliptin 5mg tablets	82575998
Gliptins	Linagliptin 5mg tablets	81160998
Gliptins	VILDAGLIPTIN 50mg tablets	84338998
Gliptins	SAXAGLIPTIN 2.5mg tablets	81513998
Gliptins	SITAGLIPTIN 25mg tablets	59373979
Gliptins	Sitagliptin 100mg tablets	84640998
Gliptins	Sitagliptin 25mg tablets	59374979
Gliptins	Sitagliptin 50mg tablets	59372979
Gliptins	Vildagliptin 50mg tablets	84341998
Thiazols	PIOGLITAZONE 45mg tablets	87884998
Thiazols	Troglitazone 200mg Tablet	88528998
Thiazols	Rosiglitazone 2mg tablet	90048998
Thiazols	Pioglitazone 30mg tablets	92237997
Thiazols	Rosiglitazone 8mg tablets	89763996
Thiazols	ROSIGLITAZONE 8mg tablets	90048996
Thiazols	Troglitazone 400mg Tablet	88528996

Diabetes Drug Class	Description	drugcode
Thiazols	PIOGLITAZONE 30mg tablets	92238997
Thiazols	ROSIGLITAZONE 4mg tablets	90048997
Thiazols	Pioglitazone 15mg tablets	92237998
Thiazols	PIOGLITAZONE 15mg tablets	92238998
Thiazols	Rosiglitazone 4mg tablets	89763997
Thiazols	TROGLITAZONE 400mg tablets	88523996
Thiazols	TROGLITAZONE 200mg tablets	88523998
Thiazols	Pioglitazone 45mg tablets	87885998
SGLT-2 Inhibs	Dapagliflozin 5mg tablets	53326979
SGLT-2 Inhibs	Dapagliflozin 10mg tablets	53328979
SGLT-2 Inhibs	DAPAGLIFLOZIN 10mg tablets	53327979
SGLT-2 Inhibs	DAPAGLIFLOZIN 5mg tablets	53325979
Meglitinides	NATEGLINIDE 60mg tablets	88131998
Meglitinides	Nateglinide 180mg tablets	88132996
Meglitinides	NATEGLINIDE 120mg tablets	88131997
Meglitinides	NATEGLINIDE 180mg tablets	88131996
Meglitinides	Nateglinide 120mg tablets	88132997
Meglitinides	Repaglinide 1mg tablets	91924997
Meglitinides	Repaglinide 500microgram tablets	91924998
Meglitinides	REPAGLINIDE 1mg tablets	85267998
Meglitinides	Repaglinide 500microgram tablets	92999979
Meglitinides	REPAGLINIDE 0.5mg tablets	85268998
Meglitinides	REPAGLINIDE 2mg tablets	85266998
Meglitinides	Repaglinide 2mg tablets	91924996
Meglitinides	Nateglinide 60mg tablets	88132998
Meglitinides	Repaglinide 500microgram tablets	91908990
Meglitinides	REPAGLINIDE 1mg tablets	91923997
Meglitinides	REPAGLINIDE 2mg tablets	91923996
Meglitinides	REPAGLINIDE 0.5mg tablets	91923998
Oral Combinations	Linagliptin 2.5mg / Metformin 850mg tablets	54905979
Oral Combinations	LINAGLIP/METFORM 2.5/850mg tab	54904979
Oral Combinations	VILDA/METFORMIN 50/850mg tabs	84009998
Oral Combinations	Rosiglitazone 2mg / Metformin 1g tablets	87182998
Oral Combinations	ROSIGL 2mg/METFRMN 1000mg tab	87180998
Oral Combinations	Metformin with rosiglitazone 500mg + 1mg Tablet	87774998
Oral Combinations	Pioglitazone 15mg / Metformin 850mg tablets	85625998
Oral Combinations	Metformin with rosiglitazone 1000mg + 2mg Tablet	87166998
Oral Combinations	ROSIGL 4mg/METFRMN 1000mg tab	87179998
Oral Combinations	Vildagliptin 50mg / Metformin 850mg tablets	84011998
Oral Combinations	Rosiglitazone 4mg / Metformin 1g tablets	87181998
Oral Combinations	Metformin with rosiglitazone 1000mg + 4mg Tablet	87165998
Oral Combinations	Metformin with rosiglitazone 500mg + 2mg Tablet	87772998
Oral Combinations	Metformin 1g / Sitagliptin 50mg tablets	83401998
Oral Combinations	ROSIGLTZO/METFRMN 1/500mg tab	87771998
Oral Combinations	Rosiglitazone 1mg / Metformin 500mg tablets	87775998
Oral Combinations	Metformin with pioglitazone 850mg + 15mg Tablet	85624998
Oral Combinations	SITAG/METFORMIN 50/1000mg tabs	82068998

Diabetes Drug Class	Description	drugcode
Oral Combinations	ROSIGLTZN/METFRMN 2/500mg tab	87770998
Oral Combinations	LINGLIP/METFORM 2.5/1000mg tab	54906979
Oral Combinations	Linagliptin 2.5mg / Metformin 1g tablets	54907979
Oral Combinations	Rosiglitazone 2mg / Metformin 500mg tablets	87773998
Oral Combinations	METFMN 850mg/PIOGLIT 15mg tabs	85622998
Oral Combinations	VILDA/METFORMIN 50/1000mg tabs	84008998
Oral Combinations	Vildagliptin 50mg / Metformin 1g tablets	84010998

Supplementary Table 4A3 Additional Health Record (AHD) Code List used to identify individuals with diabetes mellitus

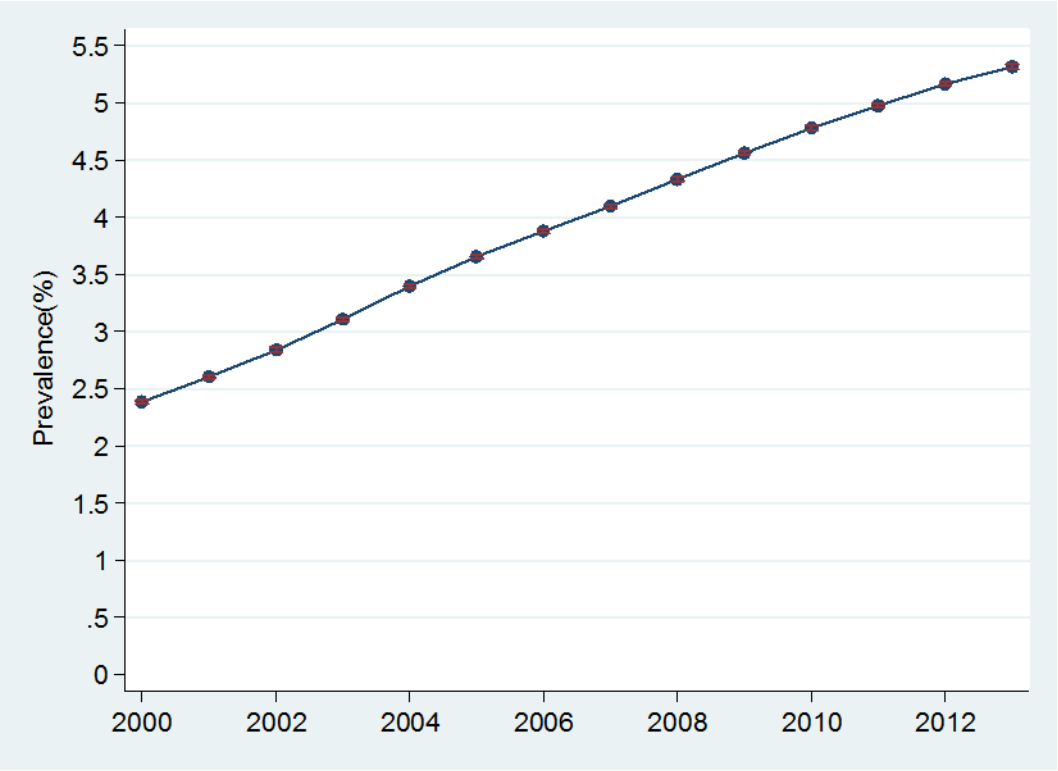
Description	ahdcode
hba1c - diabetic control	1001400140
diabetic retinopathy screening	1001400327
diabetes annual check	1009100000
diabetes current status	1009111000
diabetes insulin dosage	1009120000

Supplementary Table 4A4 Read Code List used to identify diabetes mellitus subtypes to exclude

Description	Read code
maturity onset diabetes in youth	C10C.11
latent autoimmune diabetes mellitus in adult	C10ER00
steroid induced diabetes	C11y000
gestational diabetes mellitus	L180811
gestational diabetes mellitus	L180900
syndrome of infant of mother with gestational diabetes	Q44B.00
dietary advice for gestational diabetes	ZC2CB00
[v]personal history of gestational diabetes mellitus	ZV13F00
secondary diabetes mellitus	C10N.00
secondary pancreatic diabetes mellitus without compli	C10G000
secondary diabetes mellitus without complication	C10N000
secondary pancreatic diabetes mellitus	C10G.00
type a insulin resistance	C10K.00
type a insulin resistance without complication	C10K000
insulin autoimmune syndrome without complication	C10J000
cystic fibrosis related diabetes mellitus	C10N100
steroid induced diabetes mellitus without complicatio	C10B000
diabetes mellitus induced by steroids	C10B.00
dm induced by non-steroid drugs without complication	C10H000
diabetes mellitus in puerperium - baby delivered	L180200
diabetes: shared care in pregnancy - diabetol and obs	66AX.00
insulin autoimmune syndrome	C10J.00
diabetes mellitus during pregnancy – baby not yet del	L180300
diabetes mellitus - unspec whether in pregnancy/puerp	L180000
diabetes mellitus, adult onset, with ketoacidotic com	C103100
diabetes mellitus, adult onset, with ketoacidosis	C101100

Appendix C. **Supplementary Material for Chapter 5**

Supplementary Figure 5A1 Incidence of type 2 diabetes mellitus



Supplementary Figure 5A2 Percentage prevalence of type 2 diabetes mellitus

Supplementary Table 5A1 Prevalence of prescribing of different anti-diabetic classes among all type 2 diabetics on medication

Year	N	Metf%(95%CI)	Sulf%(95%CI)	Ins%(95%CI)	Glipt%(95%CI)	Thiazol%(95%CI)	GLP-1%(95%CI)	Megl%(95%CI)	Acar%(95%CI)	SGLT% (95%CI)
2000	48,501	55.4 (55.0 to 55.8)	64.8 (64.3 to 65.2)	20.4 (20.0 to 20.7)	-	1.2 (1.1 to 1.3)	-	0.9 (0.8 to 1.0)	4.2 (4.0 to 4.4)	-
2001	54,339	59.5 (59.1 to 59.9)	61.2 (60.8 to 61.6)	21.4 (21.0 to 21.7)	-	5.4 (5.2 to 5.6)	-	1.2 (1.1 to 1.3)	3.3 (3.1 to 3.4)	-
2002	60,454	63.9 (63.5 to 64.2)	56.7 (56.3 to 57.1)	21.7 (21.4 to 22.1)	-	7.8 (7.6 to 8.0)	-	1.7 (1.6 to 1.8)	2.7 (2.5 to 2.8)	-
2003	65,828	67.8 (67.4 to 68.1)	53.0 (52.6 to 53.4)	22.6 (22.3 to 22.9)	-	10.6 (10.3 to 10.8)	-	1.6 (1.5 to 1.7)	2.2 (2.1 to 2.3)	-
2004	72,054	71.3 (71.0 to 71.6)	49.5 (49.2 to 49.9)	23.4 (23.1 to 23.7)	-	13.1 (12.8 to 13.3)	-	1.4 (1.3 to 1.5)	1.8 (1.7 to 1.9)	-
2005	77,384	73.4 (73.1 to 73.7)	47.0 (46.6 to 47.3)	23.7 (23.4 to 24.0)	-	14.9 (14.6 to 15.1)	-	1.1 (1.1 to 1.2)	1.5 (1.4 to 1.5)	-
2006	82,186	74.3 (74.0 to 74.6)	45.1 (44.7 to 45.4)	23.7 (23.4 to 23.9)	-	15.9 (15.7 to 16.2)	-	0.9 (0.8 to 1.0)	1.2 (1.1 to 1.3)	-
2007	86,871	75.0 (74.8 to 75.3)	43.9 (43.6 to 44.2)	23.5 (23.2 to 23.8)	0.2 (0.2 to 0.2)	16.0 (15.8 to 16.3)	0.1 (0.1 to 0.2)	0.9 (0.8 to 0.9)	1.0 (0.9 to 1.0)	-
2008	89,903	77.1 (76.9 to 77.4)	43.8 (43.5 to 44.1)	23.5 (23.3 to 23.8)	1.2 (1.1 to 1.2)	14.7 (14.4 to 14.9)	0.8 (0.8 to 0.9)	0.9 (0.8 to 0.9)	0.8 (0.7 to 0.9)	-
2009	93,041	79.0 (78.8 to 79.3)	43.7 (43.4 to 44.1)	23.3 (23.0 to 23.6)	3.6 (3.5 to 3.7)	13.9 (13.7 to 14.1)	2.0 (1.9 to 2.1)	0.8 (0.7 to 0.8)	0.7 (0.6 to 0.7)	-
2010	93,408	81.5 (81.2 to 81.7)	43.4 (43.1 to 43.7)	22.8 (22.6 to 23.1)	7.6 (7.5 to 7.8)	13.6 (13.4 to 13.8)	3.4 (3.3 to 3.5)	0.7 (0.6 to 0.7)	0.6 (0.5 to 0.6)	-
2011	94,025	82.6 (82.3 to 82.8)	42.8 (42.5 to 43.1)	22.8 (22.5 to 23.1)	10.5 (10.3 to 10.7)	11.7 (11.5 to 11.9)	4.3 (4.2 to 4.4)	0.6 (0.5 to 0.6)	0.5 (0.4 to 0.5)	-
2012	93,888	83.1 (82.8 to 83.3)	42.3 (41.9 to 42.6)	23.1 (22.8 to 23.3)	13.4 (13.2 to 13.6)	9.9 (9.7 to 10.1)	5.0 (4.8 to 5.1)	0.5 (0.5 to 0.5)	0.4 (0.4 to 0.5)	-
2013	91,619	83.6 (83.4 to 83.8)	41.4 (41.1 to 41.7)	23.3 (23.0 to 23.6)	15.4 (15.2 to 15.7)	8.5 (8.3 to 8.7)	5.3 (5.2 to 5.5)	0.5 (0.4 to 0.5)	0.4 (0.3 to 0.4)	0.5 (0.5 to 0.6)

N=Total number of Type 2 diabetics in a calendar year prescribed any anti-diabetic medicines, Metf=metformin, Sulf=sulphonylurea, Ins=Insulins, Glipt=gliptins, Thiazol=thiazolidinediones, GLP-1=glucagon-like-peptide-1 analogues, Megl=meglitinides, Acar=acarbose, SGLT=sodium-glucose co-transporter2 inhibitors

Supplementary Table 5A2 Prevalence of prescribing of different anti-diabetic classes used to initiate treatment in newly diagnosed type 2 diabetics.

Year	N	Metf%(95%CI)	Sulf%(95%CI)	Ins%(95%CI)	Glipt%(95%CI)	Thiazol%(95%CI)	GLP-1%(95%CI)	Megl%(95%CI)	Acar%(95%CI)	SGLT%(95%CI)
2000	2,574	45.1 (43.2 to 47.1)	51.1 (49.2 to 53.0)	3.1 (2.4 to 3.7)	-	-	-	0.5 (0.3 to 0.8)	0.2 (0 to 0.3)	-
2001	4,385	56.6 (55.1 to 58.0)	40.0 (38.6 to 41.5)	2.8 (2.3 to 3.3)	-	0.1 (0 to 0.2)	-	0.3 (0.1 to 0.4)	0.2 (0.1 to 0.3)	-
2002	5,859	66.3 (65.1 to 67.5)	29.8 (28.6 to 31.0)	2.9 (2.5 to 3.4)	-	0.4 (0.3 to 0.6)	-	0.4 (0.2 to 0.6)	0.1 (0 to 0.2)	-
2003	7,192	74.5 (73.5 to 75.5)	21.6 (20.7 to 22.6)	2.9 (2.5 to 3.3)	-	0.6 (0.4 to 0.8)	-	0.2 (0.1 to 0.3)	0.2 (0.1 to 0.3)	-
2004	8,885	79.5 (78.6 to 80.3)	16.4 (15.6 to 17.1)	2.7 (2.3 to 3.0)	-	1.1 (0.9 to 1.3)	-	0.2 (0.1 to 0.3)	0.2 (0.1 to 0.3)	-
2005	9,416	82.1 (81.3 to 82.9)	14.1 (13.4 to 14.8)	2.4 (2.1 to 2.7)	-	1.1 (0.9 to 1.3)	-	0.1 (0 to 0.2)	0.1 (0.1 to 0.2)	-
2006	9,841	84.4 (83.7 to 85.1)	12.0 (11.4 to 12.7)	2.5 (2.2 to 2.9)	-	0.9 (0.7 to 1.1)	-	0.1 (0 to 0.1)	0.2 (0.1 to 0.2)	-
2007	10,763	86.9 (86.2 to 87.5)	10.2 (9.6 to 10.7)	2.3 (2.0 to 2.6)	-	0.5 (0.4 to 0.6)	-	0.1 (0 to 0.2)	0.1 (0 to 0.1)	-
2008	11,090	87.5 (86.9 to 88.1)	9.7 (9.2 to 10.3)	2.4 (2.1 to 2.6)	-	0.2 (0.1 to 0.3)	-	0.1 (0 to 0.1)	0.1 (0 to 0.1)	-
2009	12,311	89.1 (88.6 to 89.7)	8.7 (8.2 to 9.2)	1.8 (1.5 to 2.0)	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.2)	0.1 (0 to 0.1)	0.1 (0 to 0.1)	-	-
2010	11,938	89.8 (89.3 to 90.4)	7.8 (7.3 to 8.2)	1.9 (1.6 to 2.1)	0.2 (0.1 to 0.3)	0.2 (0.1 to 0.2)	0.1 (0 to 0.1)	-	-	-
2011	11,168	90.2 (89.6 to 90.7)	7.7 (7.2 to 8.2)	1.7 (1.5 to 1.9)	0.3 (0.2 to 0.4)	0.1 (0.0 to 0.1)	0.1 (0 to 0.1)	-	-	-
2012	11,271	90.4 (89.9 to 90.9)	7.4 (6.9 to 7.9)	1.5 (1.2 to 1.7)	0.5 (0.4 to 0.7)	-	0.1 (0 to 0.1)	-	0.1 (0 to 0.1)	-
2013	10,830	91.0 (90.5 to 91.5)	6.3 (5.9 to 6.8)	1.7 (1.4 to 1.9)	0.8 (0.7 to 1.0)	0.1 (0. to 0.1)	-	-	-	-

N=Total number of newly diagnosed Type 2 diabetics in a calendar year initiated on anti-diabetic medicines, Metf=metformin, Sulf=sulphonylurea, Ins=Insulins, Glipt=gliptins, Thiazol=thiazolidinediones, GLP-1=glucagon-like-peptide-1 analogues, Megl=meglitinides, Acar=acarbose, SGLT=sodium-glucose co-transporter2 inhibitors

Supplementary Table 5A3 Prevalence of prescribing of different anti-diabetic classes used as add-on agents in type 2 diabetics on metformin.

Year	N	Sulf%(95%CI)	Ins%(95%CI)	Glipt%(95%CI)	Thiazol%(95%CI)	GLP-1%(95%CI)	Megl%(95%CI)	Acar%(95%CI)	SGLT%(95%CI)
2000	640	75.9 (72.6 to 79.3)	0.8 (0.1 to 1.5)	1.3 (0.4 to 2.1)	18.8 (15.7 to 21.8)	-	2.2 (1.1 to 3.3)	1.1 (0.3 to 1.9)	-
2001	1,355	68.6 (66.2 to 71.1)	1.4 (0.8 to 2.0)	2.0 (1.2 to 2.7)	24.0 (21.7 to 26.3)	0.2 (0 to 0.5)	3.2 (2.2 to 4.1)	0.6 (0.2 to 1)	-
2002	2,067	66.0 (64.0 to 68.1)	1.3 (0.8 to 1.8)	2.5 (1.8 to 3.1)	26.9 (25.0 to 28.8)	0.3 (0.1 to 0.6)	2.4 (1.8 to 3.1)	0.5 (0.2 to 0.8)	-
2003	2,670	66.7 (64.9 to 68.5)	1.7 (1.2 to 2.2)	3.9 (3.2 to 4.7)	26.5 (24.8 to 28.2)	0.3 (0.1 to 0.6)	0.8 (0.5 to 1.1)	0.1 (0 to 0.2)	-
2004	3,330	67.6 (66.0 to 69.2)	1.9 (1.5 to 2.4)	4.9 (4.1 to 5.6)	24.2 (22.7 to 25.7)	0.5 (0.2 to 0.7)	0.6 (0.3 to 0.8)	0.1 (0 to 0.2)	0.2 (0.1 to 0.4)
2005	3,478	68.1 (66.6 to 69.7)	1.7 (1.3 to 2.2)	7.4 (6.6 to 8.3)	21.6 (20.2 to 23.0)	0.5 (0.3 to 0.8)	0.5 (0.3 to 0.7)	-	0.1 (0 to 0.1)
2006	3,646	68.2 (66.6 to 69.7)	1.8 (1.4 to 2.3)	10.5 (9.5 to 11.5)	18.1 (16.9 to 19.4)	0.8 (0.5 to 1.1)	0.4 (0.2 to 0.6)	0.1 (0 to 0.2)	0 (0 to 0.1)
2007	3,976	72.5 (71.1 to 73.9)	2.3 (1.8 to 2.8)	13.0 (12.0 to 14.1)	10.5 (9.6 to 11.5)	1.0 (0.7 to 1.3)	0.5 (0.2 to 0.7)	0.1 (0 to 0.2)	0.1 (0 to 0.2)
2008	3,955	69.3 (67.8 to 70.7)	2.0 (1.6 to 2.5)	17.2 (16.1 to 18.4)	9.4 (8.5 to 10.3)	1.4 (1.0 to 1.7)	0.4 (0.2 to 0.6)	-	0.2 (0.1 to 0.3)
2009	3,952	66.4 (64.9 to 67.9)	2.4 (1.9 to 2.9)	22.8 (21.5 to 24.2)	6.1 (5.4 to 6.9)	1.5 (1.1 to 1.9)	0.3 (0.1 to 0.4)	0.1 (0 to 0.2)	0.3 (0.2 to 0.5)
2010	3,273	64.1 (62.4 to 65.7)	2.3 (1.8 to 2.8)	25.5 (24.0 to 27.0)	4.9 (4.2 to 5.7)	2.1 (1.6 to 2.6)	0.3 (0.1 to 0.5)	-	0.8 (0.5 to 1.1)
2011	2,652	64.6 (62.7 to 66.4)	3.7 (3.0 to 4.5)	25.6 (23.9 to 27.2)	3.1 (2.4 to 3.7)	1.8 (1.3 to 2.4)	0.2 (0 to 0.4)	-	1.0(0.6 to 1.4)
2012	2,119	63.9 (61.9 to 65.9)	4.1 (3.2 to 4.9)	26.2 (24.3 to 28.1)	2.2 (1.6 to 2.8)	1.8 (1.3 to 2.4)	0.2 (0 to 0.4)	0.1 (0 to 0.2)	1.5 (1.0 to 2.0)
2013	1,440	61.7 (59.2 to 64.2)	3.8 (2.8 to 4.8)	26.9 (24.7 to 29.2)	1.9 (1.2 to 2.7)	1.3 (0.7 to 1.9)	0.1 (0 to 0.3)	0.1 (0 to 0.2)	4.0 (3.0 to 5.0)

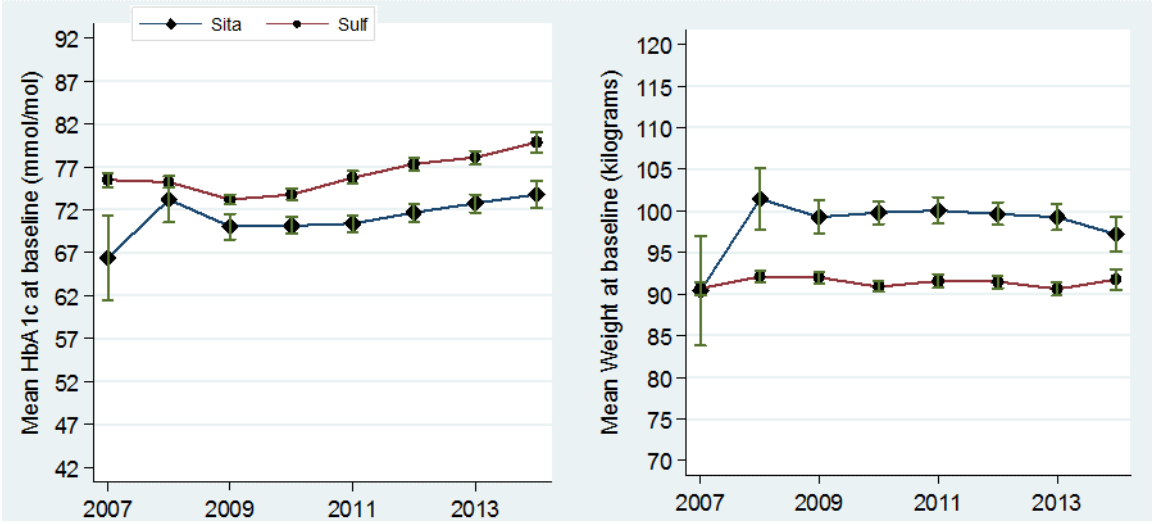
N= Total number of newly diagnosed Type 2 diabetics in a calendar year initiated on metformin who were subsequently prescribed add-on therapy, Sulf=sulphonylurea, Ins=Insulins, Glipt=gliptins, Thiazol=thiazolidinediones, GLP-1=glucagon-like-peptide-1 analogues, Megl=meglitinides, Acar=acarbose, SGLT=sodium-glucose co-transporter2 inhibitors

Supplementary Table 5A4 Prevalence of prescribing of different anti-diabetic classes used as add-on agents in type 2 diabetics on sulphonylureas.

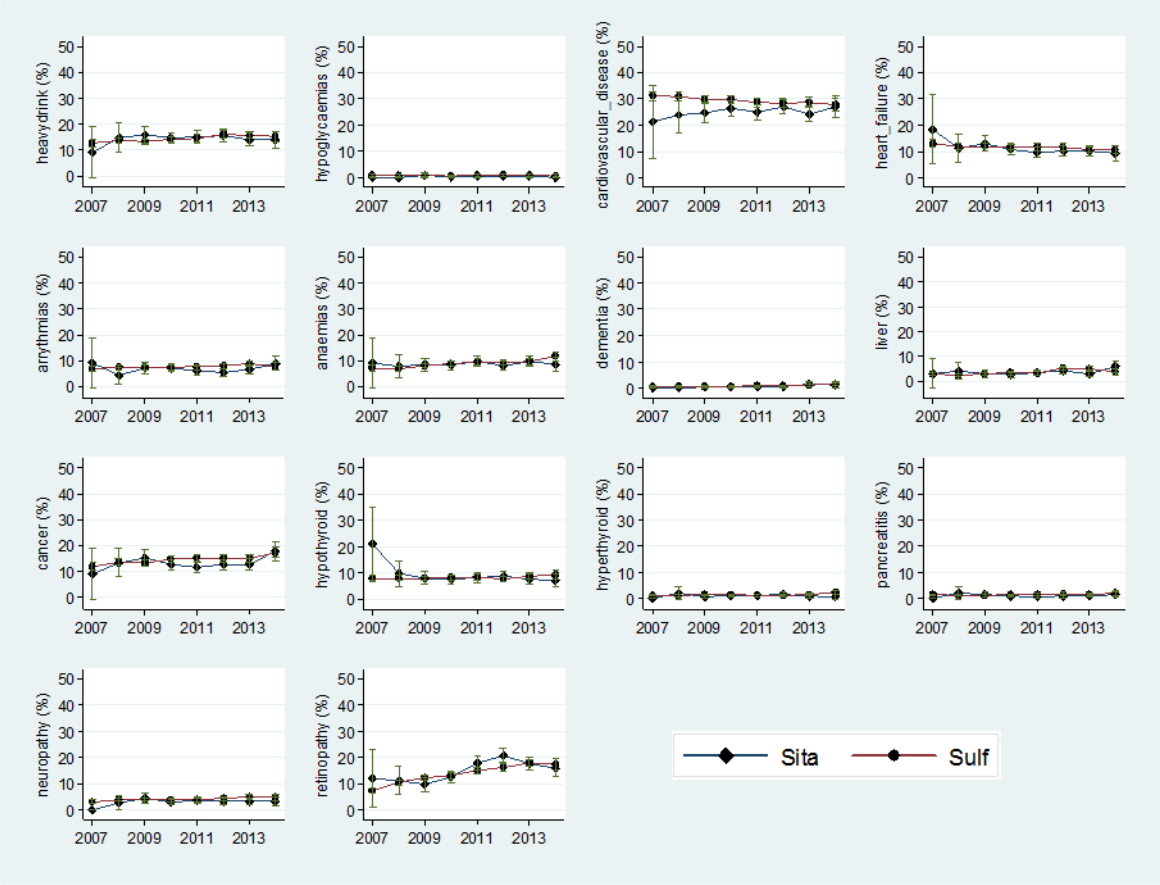
Year	N	Metf%(95%CI)	Ins%(95%CI)	Glipt%(95%CI)	Thiazol%(95%CI)	GLP-1%(95%CI)	Megl%(95%CI)	Acar%(95%CI)	SGLT%(95%CI)
2000	747	89.8 (87.7 to 92.0)	3.7 (2.4 to 5.1)	0.4 (0 to 0.9)	5.5 (3.9 to 7.1)	-	0.3 (0 to 0.6)	0.3 (0 to 0.6)	-
2001	940	89.1 (87.2 to 91.1)	5.0 (3.6 to 6.4)	0.6 (0.1 to 1.1)	4.4 (3.1 to 5.7)	-	0.5 (0.1 to 1)	0.3 (0 to 0.7)	-
2002	904	86.5 (84.3 to 88.7)	4.8 (3.4 to 6.1)	0.2 (0 to 0.5)	7.9 (6.1 to 9.6)	-	0.4 (0 to 0.9)	0.2 (0 to 0.5)	-
2003	793	84.4 (81.8 to 86.9)	6.9 (5.2 to 8.7)	0.3 (0 to 0.6)	7.9 (6.1 to 9.8)	-	0.4 (0 to 0.8)	0.1 (0 to 0.4)	-
2004	705	83.5 (80.8 to 86.3)	7.7 (5.7 to 9.6)	0.9 (0.2 to 1.5)	7.7 (5.7 to 9.6)	-	0.1 (0 to 0.4)	0.1 (0 to 0.4)	-
2005	622	84.9 (82.1 to 87.7)	7.1 (5.1 to 9.1)	1.1 (0.3 to 2.0)	6.3 (4.4 to 8.2)	-	0.6 (0 to 1.3)	-	-
2006	521	81.8 (78.4 to 85.1)	10.4 (7.7 to 13.0)	2.3 (1.0 to 3.6)	4.8 (3.0 to 6.6)	-	0.6 (0 to 1.2)	0.2 (0 to 0.6)	-
2007	479	81.2 (77.7 to 84.7)	10.6 (7.9 to 13.4)	2.7 (1.3 to 4.2)	5.0 (3.1 to 7.0)	-	0.4 (0 to 1.0)	-	-
2008	421	84.6 (81.1 to 88.0)	6.9 (4.5 to 9.3)	3.3 (1.6 to 5.0)	4.3 (2.3 to 6.2)	-	0.7 (0 to 1.5)	0.2 (0 to 0.7)	-
2009	405	84.7 (81.2 to 88.2)	9.9 (7.0 to 12.8)	3.2 (1.5 to 4.9)	2.0 (0.6 to 3.3)	-	0.2 (0 to 0.7)	-	-
2010	352	77.8 (73.5 to 82.2)	11.9 (8.5 to 15.3)	8.8 (5.8 to 11.8)	1.4 (0.2 to 2.7)	-	-	-	-
2011	319	82.8 (78.6 to 86.9)	7.2 (4.4 to 10.1)	8.8 (5.7 to 11.9)	0.9 (0 to 2.0)	0.3 (0 to 0.9)	-	-	-
2012	314	81.2 (76.9 to 85.5)	11.5 (7.9 to 15.0)	5.1 (2.7 to 7.5)	2.2 (0.6 to 3.9)	-	-	-	-
2013	239	79.9 (74.8 to 85.0)	13.4 (9.1 to 17.7)	6.3 (3.2 to 9.4)	0.4 (0 to 1.2)	-	-	-	-

N=Total number of newly diagnosed Type 2 diabetics in a calendar year initiated on sulphonylureas who were subsequently prescribed add-on therapy; Metf=metformin, Ins=Insulins, Glipt=gliptins, Thiazol=thiazolidinediones, GLP-1=glucagon-like-peptide-1 analogues, Megl=meglitinides, Acar=acarbose, SGLT=sodium-glucose co-transporter2 inhibitors

Appendix D. **Supplementary Material for Chapter 6**

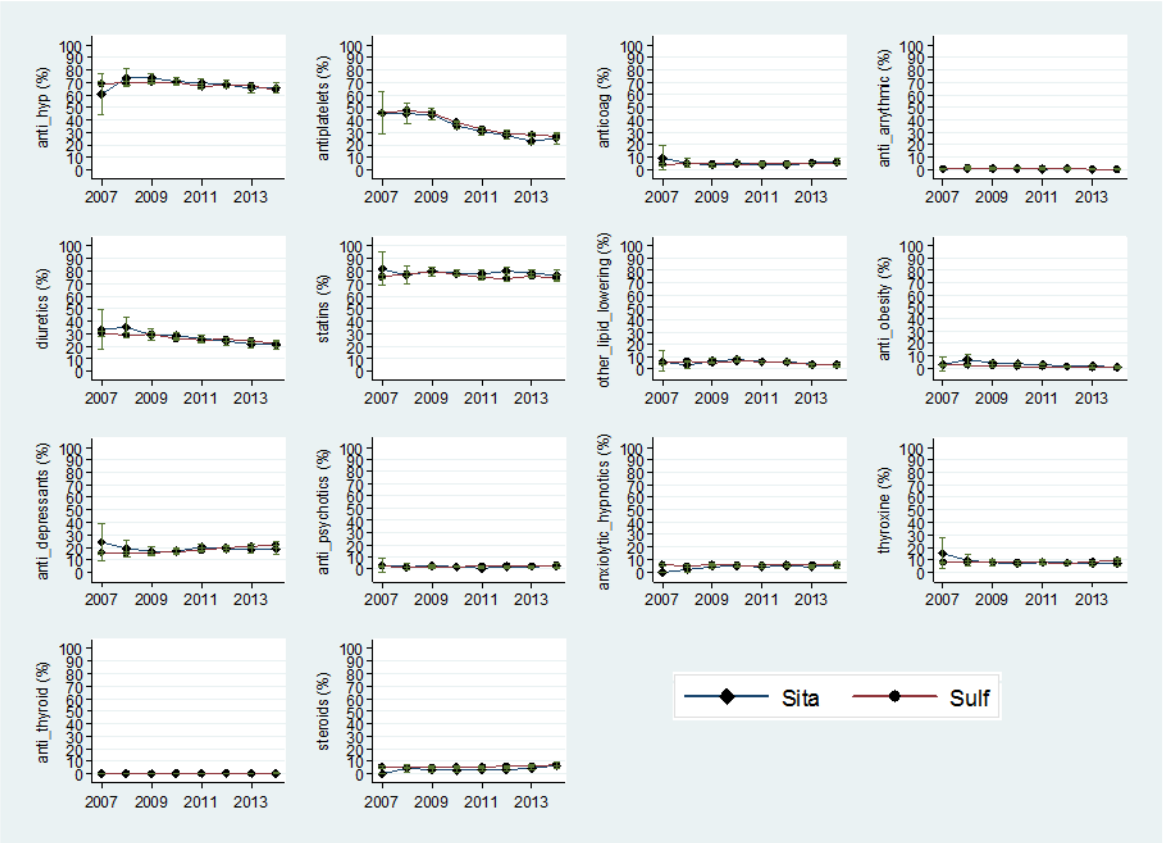


Supplementary Figure 6A1 Temporal trends in mean HbA1c (mmol/mol) and mean weight (kg) at index date (baseline) among individuals prescribed sitagliptin and sulphonylureas



Supplementary Figure 6A2 Temporal trends in comorbidities at index date among individuals prescribed sitagliptin and sulphonylureas

*Heavydrink refers to those with a history of excessive alcohol intake at the index date defined as intake of >35 units of alcohol a week for males or >28units for females



Supplementary Figure 6A3 Temporal trends in concomitantly prescribed medications within 3 months prior to index date among individuals prescribed sitagliptin and sulphonylurea

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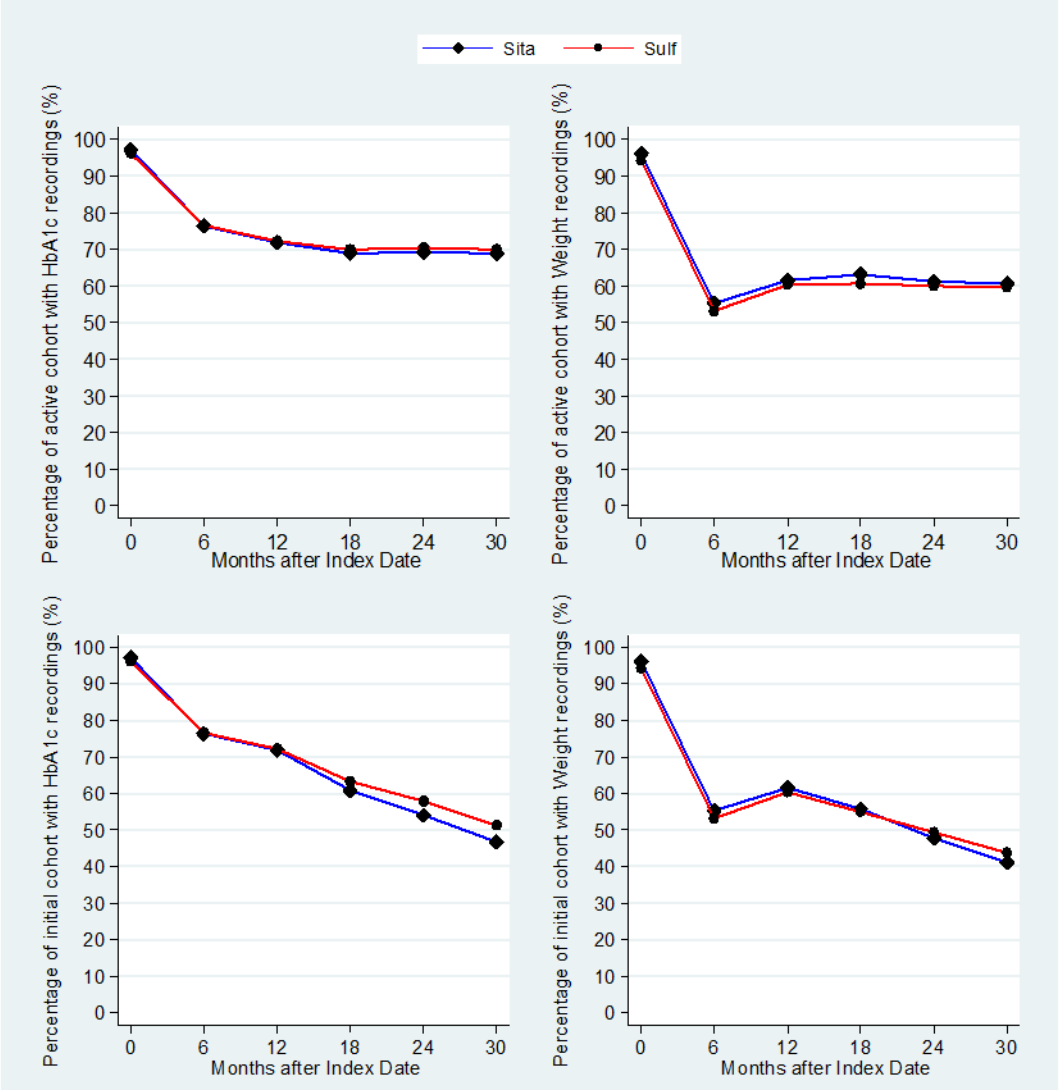
. logit sita age_entry year_entry i.sex i.townsend i.smoke weight hba1c chol sysbp diasbp metf_dose i.heavydrink i.hypoglycaemias
> i.cvd i.hf_new i.anaemias i.dementia i.ckd_stage i.liver i.arrythmias i.cancer i.hypothyroid i.hyperthyroid i.pancreatitis i.neu
> ropathy i.retinopathy i.anti_hyp i.antiplatelets i.anticoag i.anxiolytic_hypnotics i.anti_arrythmic i.diuretics i.statins i.othe
> r_lipid_lowering i.anti_depressants i.anti_psychotics i.anti_obesity i.steroids i.thyroxine i.anti_thyroid, or

Logistic regression                             Number of obs   =      23035
                                                LR chi2(45)     =    2139.00
                                                Prob > chi2     =     0.0000
Log likelihood = -9678.6469                     Pseudo R2       =     0.0995
```

sita	Odds Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
age_entry	.9916482	.0020948	-3.97	0.000	.9875508	.9957625
year_entry	1.365988	.0134688	31.63	0.000	1.339843	1.392643
2.sex	1.384806	.0589564	7.65	0.000	1.273944	1.505317
townsend						
2	.8417623	.0464475	-3.12	0.002	.7554767	.9379028
3	.8244137	.0453377	-3.51	0.000	.7401749	.9182396
4	.7827252	.0441132	-4.35	0.000	.7008691	.8741414
5	.7743189	.0476854	-4.15	0.000	.6862775	.873655
smoke						
Ex-smoker	1.031927	.0450225	0.72	0.471	.9473522	1.124052
Current smoker	.9646959	.046468	-0.75	0.456	.8777874	1.060209
weight	1.020264	.0009903	20.67	0.000	1.018325	1.022207
hba1c	.981492	.0011893	-15.42	0.000	.9791638	.9838257
chol	.9756337	.0181897	-1.32	0.186	.940626	1.011944
sysbp	.9940963	.0015502	-3.80	0.000	.9910625	.9971394
diasbp	1.005674	.002485	2.29	0.022	1.000816	1.010557
metf_dose	.9727403	.043266	-0.62	0.534	.8915318	1.061346
1.heavydrink	1.032194	.0542116	0.60	0.546	.931227	1.144108
1.hypoglycaemias	.7226431	.1681853	-1.40	0.163	.4579503	1.140327
1.cvd	.9394883	.0449295	-1.31	0.192	.8554292	1.031807
1.hf_new	1.020062	.0746936	0.27	0.786	.8836856	1.177485
1.anaemias	.9902638	.06615	-0.15	0.884	.868741	1.128786
1.dementia	1.376834	.3166855	1.39	0.164	.8771961	2.161058
ckd_stage						
1	.7807092	.0470001	-4.11	0.000	.6938177	.8784826
2	.5770138	.3489258	-0.91	0.363	.1763829	1.887626
1.liver	.7883977	.077761	-2.41	0.016	.6498153	.9565348
1.arrythmias	.8903509	.0803417	-1.29	0.198	.746023	1.062601
1.cancer	.9309629	.0508658	-1.31	0.190	.8364203	1.036192
1.hypothyroid	1.40025	.2811748	1.68	0.094	.9446734	2.075533
1.hyperthyroid	.7986945	.142323	-1.26	0.207	.5632501	1.132557
1.pancreatitis	.892925	.1533922	-0.66	0.510	.6376616	1.250373
1.neuropathy	.8387117	.0833716	-1.77	0.077	.690239	1.019121
1.retinopathy	1.09955	.0547593	1.91	0.057	.9972953	1.212289
1.anti_hyp	1.005616	.0456646	0.12	0.902	.9199826	1.099221
1.antiplatelets	.9303196	.0416409	-1.61	0.107	.8521823	1.015621
1.anticoag	1.151347	.1293177	1.25	0.210	.9238474	1.434868
1.anxiolytic_hypnotics	.922773	.083495	-0.89	0.374	.7728155	1.101828
1.anti_arrythmic	1.019139	.2599674	0.07	0.941	.618165	1.680206
1.diuretics	1.017852	.0504327	0.36	0.721	.9236536	1.121657
1.statins	1.11673	.0536318	2.30	0.022	1.016409	1.226953
1.other_lipid_lowering	1.185778	.0967533	2.09	0.037	1.010531	1.391416
1.anti_depressants	.9069914	.0463302	-1.91	0.056	.8205835	1.002498
1.anti_psychotics	.9132495	.1247697	-0.66	0.507	.6987098	1.193664
1.anti_obesity	1.575799	.2057962	3.48	0.000	1.219931	2.035476
1.steroids	.6988145	.0671212	-3.73	0.000	.5789005	.8435675
1.thyroxine	.6655404	.1360444	-1.99	0.046	.4458397	.9935051
1.anti_thyroid	.8631774	.5054882	-0.25	0.802	.2739208	2.720039
_cons	1.6e-273	3.1e-272	-31.68	0.000	2.1e-290	1.2e-256

Supplementary Figure 6A4 Logistic regression analysis to determine individual characteristics affecting propensity to be prescribed sitagliptin as opposed to a sulphonylurea

Appendix E. **Supplementary Material for Chapter 7**



Supplementary Figure 7A1 Percentage of individuals with HbA1c and weight recordings over time (6 monthly intervals) of those that are active in each respective 6 monthly period (top graphs) and of initial cohort (bottom two graphs)

*active refers to those patients that are still registered in THIN database at that point (i.e. not left practice, died

Appendix F. **Supplementary Material for Chapter 9**

Supplementary Table 9A1 Regression Analysis for mean difference in HbA1c (mmol/mol) approximately 12 months after baseline for individuals aged ≥ 18 using parsimonious model

	Unadjusted, mean diff (95% CI)	**Adjusted for baseline HbA1c, mean diff (95% CI)**	**Adjusted for Sex, Age, Baseline HbA1c, mean diff (95% CI)**	**Fully Adjusted Multivariable, mean diff (95% CI)**
Treatment				
Sulphonylurea	Ref	Ref	Ref	Ref
Sitagliptin	**0.55 (-0.04 to 1.13)**	**1.78 (1.23 to 2.33)**	**1.13 (0.59 to 1.67)**	**0.89 (0.33 to 1.45)**
Additional Covariates				
Baseline HbA1c (mmol/mol)		0.31 (0.3 to 0.32)	0.28 (0.27 to 0.3)	0.28 (0.27 to 0.3)
Age at index date (years)			-0.22 (-0.23 to -0.2)	-0.2 (-0.22 to -0.18)
Sex				
Male			Ref	Ref
Female			1.69 (1.28 to 2.11)	1.58 (1.12 to 2.04)
Year Entry				
2007				Ref
2008				-0.51 (-1.36 to 0.34)
2009				0.14 (-0.67 to 0.95)
2010				0.04 (-0.77 to 0.85)
2011				0.75 (-0.09 to 1.58)
2012				0.6 (-0.25 to 1.46)
2013				-0.05 (-0.94 to 0.83)
2014				-0.02 (-1.97 to 1.93)
Baseline Weight (kg)				0.02 (0.01 to 0.03)
F2FC*				0.08 (0.04 to 0.12)
Townsend Quintile				
1				Ref
2				0.52 (-0.09 to 1.14)
3				0.52 (-0.1 to 1.14)
4				0.85 (0.22 to 1.48)
5				1.6 (0.92 to 2.29)
Smoker				
Non				Ref
Ex				0.1 (-0.39 to 0.58)
Current				1.1 (0.57 to 1.63)
Metformin Dose at Baseline				
<1500mg				Ref
≥1500mg				0.83 (0.34 to 1.31)
Binary Comorbidity Indicator Variables				
Excessive Alcohol Intake**				-1.54 (-2.13 to -0.95)
History of Hypoglycaemia				2.03 (-0.16 to 4.22)
Neuropathy				1 (-0.06 to 2.05)
Heart failure				1.26 (0.53 to 1.99)
Anaemias				0.74 (0 to 1.48)
Liver disease				-1.4 (-2.49 to -0.31)

	Unadjusted, mean diff (95% CI)	Adjusted for baseline HbA1c, mean diff (95% CI)	Adjusted for Sex, Age, Baseline HbA1c, mean diff (95% CI)	Fully Adjusted Multivariable, mean diff (95% CI)
Binary Treatment Indicator Variables¥				
Diuretics				-1.28 (-1.8 to -0.76)
Statins				0.63 (0.13 to 1.14)
Antidepressants				1.17 (0.61 to 1.73)
Steroids –oral/iv				-1.28 (-2.22 to -0.33)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
Mean diff= mean difference, CI=confidence Interval.

Supplementary Table 9A2 Regression Analysis for mean difference in HbA1c (mmol/mol) approximately 12 months after baseline for individuals aged ≥ 18 using clinical model (based on Direct Acyclic Graph)

	Unadjusted, mean diff (95% CI)	**Adjusted for baseline HbA1c, mean diff (95% CI)**	**Adjusted for Sex, Age, Baseline HbA1c, mean diff (95% CI)**	**Fully Adjusted Multivariable, mean diff (95% CI)**
Treatment				
Sulphonylurea	**Ref**	**Ref**	**Ref**	**Ref**
Sitagliptin	**0.55 (-0.04 to 1.13)**	**1.78 (1.23 to 2.33)**	**1.13 (0.59 to 1.67)**	**0.88 (0.32 to 1.45)**
Additional Covariates				
Baseline HbA1c (mmol/mol)		0.31 (0.3 to 0.32)	0.28 (0.27 to 0.3)	0.28 (0.27 to 0.3)
Age at index date (years)			-0.22 (-0.23 to -0.2)	-0.2 (-0.22 to -0.18)
Sex				
Male			Ref	Ref
Female			1.69 (1.28 to 2.11)	1.6 (1.13 to 2.07)
Baseline Weight (kg)				0.02 (0.01 to 0.03)
Year Entry				
2007				Ref
2008				-0.55 (-1.4 to 0.3)
2009				0.13 (-0.69 to 0.94)
2010				0.06 (-0.76 to 0.87)
2011				0.75 (-0.09 to 1.59)
2012				0.64 (-0.23 to 1.5)
2013				-0.01 (-0.9 to 0.89)
2014				-0.05 (-2 to 1.9)
F2FC*				0.08 (0.04 to 0.12)
Townsend Quintile				
1				Ref
2				0.52 (-0.1 to 1.14)
3				0.54 (-0.08 to 1.16)
4				0.86 (0.23 to 1.49)
5				1.63 (0.94 to 2.31)
Smoker				
Non				Ref
Ex				0.08 (-0.41 to 0.56)
Current				1.12 (0.59 to 1.65)
CKD Stage				
(CrCl>60 ml/min)				Ref
(CrCl 30-59 ml/min)				0.07 (-0.53 to 0.67)
(CrCl<30 ml/min)				1.94 (-2.38 to 6.26)
Metformin Dose at Baseline				
<1500mg				Ref
≥1500mg				0.82 (0.33 to 1.31)
Binary Comorbidity Indicator Variables				
Excessive Alcohol Intake**				-1.53 (-2.13 to -0.94)
History of Hypoglycaemia				0 (0 to 0)
Neuropathy				0.93 (-0.12 to 1.99)
Retinopathy				0.1 (-0.48 to 0.68)

	Unadjusted, mean diff (95% CI)	Adjusted for baseline HbA1c, mean diff (95% CI)	Adjusted for Sex, Age, Baseline HbA1c, mean diff (95% CI)	Fully Adjusted Multivariable, mean diff (95% CI)
Cardiovascular disease				-0.03 (-0.54 to 0.49)
Heart failure				0.9 (0.11 to 1.7)
Anaemias				0.72 (-0.02 to 1.46)
Dementia				1.82 (-0.94 to 4.58)
Liver disease				-1.38 (-2.47 to -0.29)
Arrythmias				0.4 (-0.57 to 1.36)
Cancer				0.09 (-0.5 to 0.69)
Hypothyroidism				-0.34 (-2.63 to 1.95)
Hyperthyroid				-0.42 (-2.22 to 1.39)
Pancreatitis				1.48 (-0.3 to 3.26)
Binary Treatment Indicator Variables¥				
Anti-hypertensive				-0.39 (-0.89 to 0.12)
Antiplatelets				0.37 (-0.1 to 0.85)
Anticoagulants				0.74 (-0.5 to 1.98)
Anti-arrythmic				0.51 (-2.02 to 3.04)
Diuretics				-1.17 (-1.71 to -0.63)
Statins				0.63 (0.12 to 1.15)
Other lipid lowering drugs				0.43 (-0.48 to 1.34)
Antidepressants				1.32 (0.75 to 1.9)
Antipsychotics				-1.74 (-3.24 to -0.23)
Antiobesity				0.62 (-1.03 to 2.27)
Steroids –oral/iv				-1.27 (-2.22 to -0.32)
Thyroxine				0.57 (-1.74 to 2.88)
Anti-thyroid drugs				3.81 (-2 to 9.61)
Anxiolytics				-0.55 (-1.52 to 0.43)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
Mean diff= mean difference, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 9A3 Regression Analysis for mean difference in HbA1c (mmol/mol) approximately 12 months after baseline for individuals aged ≥ 18 "adherent" to medication

	Unadjusted, mean diff (95% CI)	Adjusted for baseline HbA1c, mean diff (95% CI)	Adjusted for Sex, Age, Baseline HbA1c, mean diff (95% CI)	Fully Adjusted Multivariable, mean diff (95% CI)
Treatment				
Sulphonylurea	Ref	Ref	Ref	Ref
Sitagliptin	**-0.89 (-1.76 to -0.02)**	**0.27 (-0.56 to 1.1)**	**-0.13 (-0.95 to 0.7)**	**-1.01 (-1.86 to -0.16)**
Additional Covariates				
Baseline HbA1c (mmol/mol)		0.22 (0.2 to 0.23)	0.21 (0.19 to 0.22)	0.2 (0.18 to 0.22)
Age at index date (years)			-0.14 (-0.17 to -0.11)	-0.12 (-0.15 to -0.09)
Sex				
Male			Ref	Ref
Female			1.28 (0.65 to 1.91)	1.17 (0.48 to 1.87)
Year Entry				
2007				0 (0 to 0)
2008				-0.58 (-2.03 to 0.88)
2009				0.63 (-0.71 to 1.97)
2010				0.88 (-0.44 to 2.21)
2011				2.87 (1.53 to 4.21)
2012				3.1 (1.75 to 4.44)
2013				3.53 (2.12 to 4.94)
2014				0 (0 to 0)
Baseline Weight (kg)				0.02 (0 to 0.03)
F2FC*				-0.01 (-0.08 to 0.06)
Townsend Quintile				
1				Ref
2				0.93 (-0.01 to 1.86)
3				0.12 (-0.79 to 1.04)
4				0.58 (-0.37 to 1.53)
5				0.41 (-0.65 to 1.46)
Smoker				
Non				Ref
Ex				0.15 (-0.57 to 0.87)
Current				0.56 (-0.24 to 1.37)
Metformin Dose at Baseline				
<1500mg				Ref
≥1500mg				0.31 (-0.42 to 1.04)
Binary Comorbidity Indicator Variables				
Excessive Alcohol Intake**				-1.19 (-2.07 to -0.32)
History of Hypoglycaemia				2.2 (-1.5 to 5.89)
Neuropathy				1.19 (-0.39 to 2.78)
Heart failure				1.8 (0.72 to 2.88)
Anaemias				1.31 (0.2 to 2.42)
Liver disease				-0.05 (-1.76 to 1.66)
Binary Treatment Indicator Variables¥				
Diuretics				-1.26 (-2.01 to -0.51)

	Unadjusted, mean diff (95% CI)	Adjusted for baseline HbA1c, mean diff (95% CI)	Adjusted for Sex, Age, Baseline HbA1c, mean diff (95% CI)	Fully Adjusted Multivariable, mean diff (95% CI)
Statins				1.02 (0.21 to 1.83)
Antidepressants				1.01 (0.16 to 1.85)
Steroids –oral/iv				-0.67 (-2.09 to 0.74)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
Mean diff= mean difference, CI=confidence Interval.

Supplementary Table 9A4 Regression Analysis for mean difference in weight (kg) approximately 12 months after baseline for individuals aged 18-75 years using parsimonious model

	Unadjusted, mean diff (95% CI)	**Adjusted for baseline weight, mean diff (95% CI)**	**Adjusted for Sex, Age& Baseline weight, mean diff (95% CI)**	**Fully Adjusted Multivariable, mean diff (95% CI)**
Treatment				
Sulphonylurea	Ref	Ref	Ref	Ref
Sitagliptin	**4.9 (4.07 to 5.72)**	**-2.7 (-2.92 to -2.49)**	**-2.61 (-2.83 to -2.4)**	**-2.26 (-2.48 to -2.04)**
Additional Covariates				
Baseline Weight (kg)		0.99 (0.98 to 0.99)	0.97 (0.97 to 0.98)	0.97 (0.97 to 0.98)
Age at index date (years)			-0.04 (-0.05 to -0.03)	-0.02 (-0.03 to -0.01)
Sex				
Male			Ref	Ref
Female			-1.51 (-1.69 to -1.34)	-1.39 (-1.57 to -1.22)
Year Entry				
2007				Ref
2008				0.09 (-0.25 to 0.43)
2009				0.25 (-0.07 to 0.58)
2010				-0.08 (-0.41 to 0.24)
2011				-0.4 (-0.73 to -0.07)
2012				-0.75 (-1.09 to -0.41)
2013				-0.4 (-0.76 to -0.04)
2014				-0.63 (-1.46 to 0.2)
Baseline HbA1c (mmol/mol)				0.04 (0.04 to 0.05)
F2FC*				-0.02 (-0.04 to 0)
CKD Stage				
(Crcl>60)				Ref
(CrCl 30-59)				-0.32 (-0.58 to -0.06)
(Crcl<30)				2.08 (-3.81 to 7.97)
Binary Comorbidity Indicator Variables				
Heart failure				-0.34 (-0.64 to -0.03)
Binary Treatment Indicator Variables¥				
Anticoagulants				-0.52 (-0.98 to -0.06)
Antipsychotics				-0.67 (-1.22 to -0.12)
Steroids – oral/iv				-0.63 (-1.03 to -0.23)

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
Mean diff= mean difference, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 9A5 Regression Analysis for mean difference in weight (kg) approximately 12 months after baseline for individuals aged 18-75 years using clinical model (based on Direct Acyclic Graph)

	Unadjusted, mean diff (95% CI)	**Adjusted for baseline weight, mean diff (95% CI)**	**Adjusted for Sex, Age& Baseline weight, mean diff (95% CI)**	**Fully Adjusted Multivariable, mean diff (95% CI)**
Treatment				
Sulphonylurea	**Ref**	**Ref**	**Ref**	**Ref**
Sitagliptin	**4.94 (4.11 to 5.78)**	**-2.73 (-2.95 to -2.51)**	**-2.65 (-2.86 to -2.43)**	**-2.31 (-2.54 to -2.09)**
Additional Covariates				
Baseline Weight (kg)		0.99 (0.98 to 0.99)	0.97 (0.97 to 0.98)	0.97 (0.97 to 0.98)
Age at index date (years)			-0.04 (-0.05 to -0.03)	-0.02 (-0.03 to -0.01)
Sex				
Male			Ref	Ref
Female			-1.51 (-1.68 to -1.33)	-1.37 (-1.56 to -1.17)
Baseline HbA1c (mmol/mol)				0.05 (0.04 to 0.05)
Year Entry				
2007				Ref
2008				0.08 (-0.26 to 0.42)
2009				0.23 (-0.1 to 0.56)
2010				-0.09 (-0.42 to 0.24)
2011				-0.42 (-0.76 to -0.08)
2012				-0.74 (-1.09 to -0.39)
2013				-0.41 (-0.78 to -0.04)
2014				-0.56 (-1.41 to 0.29)
F2FC*				-0.02 (-0.03 to 0)
Townsend Quintile				
1				Ref
2				-0.03 (-0.28 to 0.23)
3				-0.04 (-0.29 to 0.22)
4				-0.12 (-0.37 to 0.14)
5				0 (-0.28 to 0.28)
Smoker				
Non				Ref
Ex				-0.11 (-0.31 to 0.09)
Current				-0.28 (-0.49 to -0.06)
CKD Stage				
(CrCl>60 ml/min)				Ref
(CrCl 30-59 ml/min)				-0.29 (-0.56 to -0.02)
(CrCl<30 ml/min)				0.91 (-6.29 to 8.1)
Metformin Dose at Baseline				
<1500mg				Ref
≥1500mg				-0.03 (-0.23 to 0.17)
Binary Comorbidity Indicator Variables				
Excessive Alcohol Intake**				0.21 (-0.02 to 0.45)
History of Hypoglycaemia				0 (0 to 0)
Neuropathy				0.13 (-0.32 to 0.58)
Retinopathy				0.31 (0.07 to 0.54)

	Unadjusted, mean diff (95% CI)	Adjusted for baseline weight, mean diff (95% CI)	Adjusted for Sex, Age& Baseline weight, mean diff (95% CI)	Fully Adjusted Multivariable, mean diff (95% CI)
Cardiovascular disease				-0.15 (-0.36 to 0.07)
Heart failure				-0.36 (-0.7 to -0.02)
Anaemias				0.19 (-0.12 to 0.5)
Dementia				-1.84 (-3.42 to -0.26)
Liver disease				0.05 (-0.39 to 0.48)
Arrythmias				-0.07 (-0.49 to 0.35)
Cancer				-0.13 (-0.38 to 0.13)
Hypothyroidism				-0.51 (-1.47 to 0.46)
Hyperthyroid				-0.19 (-0.97 to 0.59)
Pancreatitis				-0.51 (-1.25 to 0.22)
Binary Treatment Indicator Variables¥				
Anti-hypertensive				-0.08 (-0.28 to 0.12)
Antiplatelets				0.04 (-0.15 to 0.24)
Anticoagulants				-0.39 (-0.94 to 0.15)
Anti-arrythmic				-0.35 (-1.44 to 0.75)
Diuretics				0.13 (-0.1 to 0.35)
Statins				0.06 (-0.15 to 0.27)
Other lipid lowering drugs				-0.06 (-0.43 to 0.3)
Antidepressants				-0.05 (-0.28 to 0.18)
Antipsychotics				-0.65 (-1.24 to -0.07)
Antiobesity				0.32 (-0.29 to 0.94)
Steroids –oral/iv				-0.58 (-0.99 to -0.17)
Thyroxine				0.16 (-0.82 to 1.14)
Anti-thyroid drugs				0.99 (-1.52 to 3.5)
Anxiolytics				0.25 (-0.16 to 0.65)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
Mean diff= mean difference, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 9A6 Regression Analysis for mean difference in weight (kg) approximately 12 months after baseline for individuals aged 18-75 years "adherent" to medication

	Unadjusted, mean diff (95% CI)	**Adjusted for baseline weight, mean diff (95% CI)**	**Adjusted for Sex, Age& Baseline weight, mean diff (95% CI)**	**Fully Adjusted Multivariable, mean diff (95% CI)**
Treatment				
Sulphonylurea	Ref	Ref	Ref	Ref
Sitagliptin	**1.01 (-0.61 to 2.64)**	**-3.34 (-3.74 to -2.95)**	**-3.26 (-3.65 to -2.87)**	**-3.00 (-3.40 to -2.60)**
Additional Covariates				
Baseline Weight (kg)		1 (0.99 to 1)	0.98 (0.98 to 0.99)	0.98 (0.98 to 0.99)
Age at index date (years)			-0.03 (-0.05 to -0.01)	-0.01 (-0.03 to 0)
Sex				
Male			Ref	Ref
Female			-1.17 (-1.49 to -0.85)	-1.02 (-1.34 to -0.7)
Year Entry				
2007				Ref
2008				0.31 (-0.39 to 1.01)
2009				0.74 (0.09 to 1.39)
2010				0.35 (-0.29 to 1)
2011				0.37 (-0.28 to 1.01)
2012				0.19 (-0.46 to 0.85)
2013				0.46 (-0.22 to 1.15)
Baseline HbA1c (mmol/mol)				0.05 (0.04 to 0.06)
F2FC*				-0.02 (-0.06 to 0.01)
CKD Stage				
(CrCl>60 ml/min)				Ref
(CrCl 30-59 ml/min)				-0.18 (-0.64 to 0.27)
(CrCl<30 ml/min)				0 (0 to 0)
Binary Comorbidity Indicator Variables				
Heart failure				-0.43 (-0.98 to 0.13)
Binary Treatment Indicator Variables¥				
Anticoagulants				-1 (-1.85 to -0.15)
Antipsychotics				-1.16 (-2.11 to -0.21)
Steroids –oral/iv				-0.97 (-1.7 to -0.24)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
Mean diff= mean difference, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 9A7 Regression Analysis for mean difference in weight (kg) approximately 12 months after baseline for individuals aged ≥ 75 years using parsimonious model

	Unadjusted, mean diff (95% CI)	**Adjusted for baseline weight, mean diff (95% CI)**	**Adjusted for Sex, Age& Baseline weight, mean diff (95% CI)**	**Fully Adjusted Multivariable, mean diff (95% CI)**
Treatment				
Sulphonylurea	Ref	Ref	Ref	Ref
Sitagliptin	**2.73 (0.67 to 4.78)**	**-1.5 (-2.14 to -0.86)**	**-1.49 (-2.12 to -0.86)**	**-1.31 (-1.96 to -0.66)**
Additional Covariates				
Baseline Weight (kg)		0.97 (0.96 to 0.99)	0.95 (0.94 to 0.97)	0.96 (0.94 to 0.97)
Age at index date (years)			-0.16 (-0.22 to -0.11)	-0.15 (-0.21 to -0.09)
Sex				
Male			Ref	Ref
Female			-1.11 (-1.55 to -0.67)	-1.1 (-1.54 to -0.65)
Year Entry				
2007				Ref
2008				-0.75 (-1.61 to 0.1)
2009				-0.7 (-1.5 to 0.11)
2010				-0.67 (-1.47 to 0.12)
2011				-1.17 (-2 to -0.34)
2012				-1.07 (-1.94 to -0.2)
2013				-0.63 (-1.51 to 0.25)
2014				-0.4 (-2.39 to 1.58)
Baseline HbA1c (mmol/mol)				0.01 (-0.01 to 0.02)
F2FC*				-0.01 (-0.05 to 0.03)
CKD Stage				
(CrCl>60 ml/min)				Ref
(CrCl 30-59 ml/min)				-0.34 (-0.78 to 0.11)
(CrCl<30 ml/min)				1.37 (-0.36 to 3.1)
Binary Comorbidity Indicator Variables				
Heart failure				-0.36 (-0.89 to 0.18)
Binary Treatment Indicator Variables¥				
Anticoagulants				-1.32 (-2.04 to -0.6)
Antipsychotics				-1.4 (-3.45 to 0.65)
Steroids –oral/iv				0.24 (-0.49 to 0.98)

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
Mean diff= mean difference, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 9A8 Regression Analysis for mean difference in weight (kg) approximately 12 months after baseline for individuals aged ≥ 75 years using clinical model (based on Direct Acyclic Graph)

	Unadjusted, mean diff (95% CI)	Adjusted for baseline weight, mean diff (95% CI)	Adjusted for Sex, Age& Baseline weight, mean diff (95% CI)	Fully Adjusted Multivariable, mean diff (95% CI)
Treatment				
Sulphonylurea	**Ref**	**Ref**	**Ref**	**Ref**
Sitagliptin	**2.72 (0.63 to 4.8)**	**-1.56 (-2.21 to -0.9)**	**-1.55 (-2.2 to -0.91)**	**-1.38 (-2.04 to -0.72)**
Additional Covariates				
Baseline Weight (kg)		0.97 (0.96 to 0.99)	0.95 (0.94 to 0.97)	0.96 (0.94 to 0.97)
Age at index date (years)			-0.17 (-0.22 to -0.11)	-0.16 (-0.22 to -0.1)
Sex				
Male			Ref	Ref
Female			-1.2 (-1.64 to -0.75)	-1.21 (-1.7 to -0.72)
Baseline HbA1c (mmol/mol)				0 (-0.01 to 0.02)
Year Entry				
2007				Ref
2008				-0.64 (-1.49 to 0.22)
2009				-0.61 (-1.42 to 0.2)
2010				-0.68 (-1.48 to 0.11)
2011				-1.17 (-2.01 to -0.33)
2012				-1.09 (-1.97 to -0.21)
2013				-0.58 (-1.48 to 0.31)
2014				-0.37 (-2.36 to 1.62)
F2FC*				-0.01 (-0.05 to 0.03)
Townsend Quintile				
1				Ref
2				0.14 (-0.45 to 0.72)
3				0.37 (-0.25 to 0.99)
4				-0.12 (-0.77 to 0.52)
5				0.32 (-0.41 to 1.05)
Smoker				
Non				Ref
Ex				-0.17 (-0.63 to 0.29)
Current				0.68 (-0.01 to 1.36)
CKD Stage				
(CrCl>60 ml/min)				Ref
(CrCl 30-59 ml/min)				-0.27 (-0.73 to 0.18)
(CrCl<30 ml/min)				1.43 (-0.32 to 3.17)
Metformin Dose at Baseline				
<1500mg				Ref
≥1500mg				-0.16 (-0.61 to 0.3)
Binary Comorbidity Indicator Variables				
Excessive Alcohol Intake**				0.04 (-0.76 to 0.85)
History of Hypoglycaemia				0 (0 to 0)
Neuropathy				0.99 (0.15 to 1.84)
Retinopathy				0.06 (-0.49 to 0.61)

	Unadjusted, mean diff (95% CI)	Adjusted for baseline weight, mean diff (95% CI)	Adjusted for Sex, Age& Baseline weight, mean diff (95% CI)	Fully Adjusted Multivariable, mean diff (95% CI)
Cardiovascular disease				-0.08 (-0.53 to 0.37)
Heart failure				-0.44 (-1.07 to 0.19)
Anaemias				0.31 (-0.33 to 0.96)
Dementia				1.51 (0.03 to 2.98)
Liver disease				0.35 (-1.11 to 1.8)
Arrythmias				-0.01 (-0.74 to 0.72)
Cancer				0.21 (-0.26 to 0.69)
Hypothyroidism				1.84 (-0.24 to 3.92)
Hyperthyroid				-1.51 (-3.05 to 0.02)
Pancreatitis				-0.41 (-2.41 to 1.6)
Binary Treatment Indicator Variables¥				
Anti-hypertensive				0.15 (-0.46 to 0.76)
Antiplatelets				-0.19 (-0.66 to 0.27)
Anticoagulants				-1.39 (-2.31 to -0.48)
Anti-arrythmic				-0.57 (-2.58 to 1.44)
Diuretics				0.18 (-0.32 to 0.67)
Statins				-0.24 (-0.78 to 0.31)
Other lipid lowering drugs				-0.54 (-1.54 to 0.46)
Antidepressants				-0.1 (-0.74 to 0.54)
Antipsychotics				-1.63 (-3.76 to 0.5)
Antiobesity				-21 (-30.49 to -11.52)
Steroids –oral/iv				0.16 (-0.58 to 0.91)
Thyroxine				-1.4 (-3.46 to 0.67)
Anti-thyroid drugs				0.13 (-4.6 to 4.87)
Anxiolytics				-0.48 (-1.39 to 0.44)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
Mean diff= mean difference, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 9A9 Regression Analysis for mean difference in weight (kg) approximately 12 months after baseline for individuals aged ≥ 75 years "adherent" to medication

	Unadjusted, mean diff (95% CI)	**Adjusted for baseline weight, mean diff (95% CI)**	**Adjusted for Sex, Age& Baseline weight, mean diff (95% CI)**	**Fully Adjusted Multivariable, mean diff (95% CI)**
Treatment				
Sulphonylurea	Ref	Ref	Ref	Ref
Sitagliptin	**0.67 (-2.95 to 4.3)**	**-2.54 (-3.49 to -1.6)**	**-2.54 (-3.48 to -1.61)**	**-2.46 (-3.43 to -1.49)**
Additional Covariates				
Baseline Weight (kg)		0.99 (0.97 to 1.01)	0.98 (0.95 to 1)	0.97 (0.94 to 0.99)
Age at index date (years)			-0.14 (-0.22 to -0.05)	-0.12 (-0.21 to -0.04)
Sex				
Male			Ref	Ref
Female			-0.84 (-1.5 to -0.18)	-0.86 (-1.54 to -0.19)
Year Entry				
2007				Ref
2008				-0.24 (-1.64 to 1.15)
2009				-0.73 (-2.02 to 0.55)
2010				-0.53 (-1.81 to 0.75)
2011				-0.87 (-2.16 to 0.41)
2012				-0.36 (-1.67 to 0.95)
2013				-0.17 (-1.57 to 1.24)
Baseline HbA1c (mmol/mol)				0.01 (-0.01 to 0.03)
F2FC*				0 (-0.07 to 0.07)
CKD Stage				
(CrCl>60 ml/min)				Ref
(CrCl 30-59 ml/min)				-0.62 (-1.31 to 0.06)
(CrCl<30 ml/min)				-2.69 (-6.79 to 1.41)
Binary Comorbidity Indicator Variables				
Heart failure				0.29 (-0.53 to 1.1)
Binary Treatment Indicator Variables¥				
Anticoagulants				-0.55 (-1.69 to 0.6)
Antipsychotics				-3.04 (-5.35 to -0.74)
Steroids –oral/iv				-0.3 (-1.44 to 0.83)

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
Mean diff= mean difference, CrCl=Creatinine Clearance, CI=confidence Interval.

Appendix G. **Supplementary Material for Chapter 10**

Supplementary Table 10A1 Cox regression analysis for time to first recording of a HbA1c > 58 mmol/mol for individuals aged ≥ 18 years using parsimonious model

	Unadjusted (HR, 95% CI)	**Adjusted for Sex & Age (HR, 95% CI)**	**Fully Adjusted Multivariate (HR, 95% CI)**
Treatment			
Sulphonylurea	Ref	Ref	Ref
Sitagliptin	**1.09 (1.05 to 1.14)**	**1.04 (1 to 1.09)**	**1.11 (1.06 to 1.16)**
Additional Covariates			
Age at index date (years)		0.98 (0.98 to 0.98)	0.99 (0.98 to 0.99)
Sex			
Male		Ref	Ref
Female		1.12 (1.08 to 1.16)	1.15 (1.11 to 1.2)
Baseline HbA1c (mmol/mol)			1.01 (1.01 to 1.02)
Baseline Weight (kg)			1 (1 to 1)
F2FC*			1.01 (1.01 to 1.02)
Year Entry			
2007			Ref
2008			1.01 (0.94 to 1.08)
2009			0.99 (0.93 to 1.06)
2010			0.98 (0.92 to 1.05)
2011			1.04 (0.98 to 1.11)
2012			1.03 (0.96 to 1.1)
2013			0.97 (0.91 to 1.05)
2014			1.28 (1.16 to 1.42)
Smoker			
Non			Ref
Ex			1.04 (1 to 1.08)
Current			1.09 (1.05 to 1.14)
CKD Stage			
(CrCl>60 ml/min)			Ref
(CrCl 30-59 ml/min)			0.94 (0.89 to 0.99)
(CrCl<30 ml/min)			1.19 (0.82 to 1.72)
Binary Comorbidity Indicator Variables			
Hypoglycaemias			1.22 (1.03 to 1.44)
Excessive Alcohol Intake**			0.9 (0.86 to 0.94)
Heart failure			1.15 (1.08 to 1.22)
Binary Treatment Indicator Variables¥			
Diuretics			0.88 (0.84 to 0.92)
Antidepressants			1.09 (1.04 to 1.14)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 10A2 Cox regression analysis for time to first recording of a HbA1c > 58 mmol/mol for individuals aged ≥ 18 years using clinical model (based on Direct Acyclic Graph)

	Unadjusted (HR, 95% CI)	Adjusted for Sex & Age (HR, 95% CI)	Fully Adjusted Multivariate (HR, 95% CI)
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**1.1 (1.05 to 1.14)**	**1.04 (1 to 1.09)**	**1.11 (1.06 to 1.16)**
Additional Covariates			
Age at index date (years)		0.98 (0.98 to 0.98)	1.01 (1.01 to 1.02)
Sex			
Male		Ref	
Female		1.12 (1.08 to 1.15)	Ref
Baseline HbA1c (mmol/mol)			1.16 (1.12 to 1.2)
Baseline Weight (kg)			1 (1 to 1)
Year Entry			
2007			1 (0 to 0)
2008			1 (0.93 to 1.07)
2009			0.99 (0.93 to 1.06)
2010			0.97 (0.91 to 1.04)
2011			1.04 (0.97 to 1.11)
2012			1.02 (0.95 to 1.09)
2013			0.96 (0.89 to 1.04)
2014			1.28 (1.15 to 1.42)
F2FC*			1.01 (1.01 to 1.01)
Townsend Quintile			
1			Ref
2			1 (0.95 to 1.05)
3			0.98 (0.93 to 1.03)
4			1.01 (0.96 to 1.06)
5			1.05 (1 to 1.11)
Smoker			
Non			Ref
Ex			1.03 (0.99 to 1.08)
Current			1.08 (1.04 to 1.13)
CKD Stage			
(CrCl>60 ml/min)			Ref
(CrCl 30-59 ml/min)			0.94 (0.9 to 0.99)
(CrCl<30 ml/min)			1.24 (0.86 to 1.79)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			1.02 (0.98 to 1.06)
Binary Comorbidity Indicator Variables			
Excessive Alcohol Intake**			0.89 (0.85 to 0.93)
History of Hypoglycaemia			1.22 (1.02 to 1.44)
Neuropathy			1.02 (0.94 to 1.11)
Retinopathy			1.04 (0.99 to 1.09)
Cardiovascular disease			1 (0.96 to 1.04)

	Unadjusted (HR, 95% CI)	Adjusted for Sex & Age (HR, 95% CI)	Fully Adjusted Multivariate (HR, 95% CI)
Heart failure			1.12 (1.05 to 1.2)
Anaemias			1.06 (1 to 1.12)
Dementia			1.22 (0.98 to 1.52)
Liver disease			1 (0.92 to 1.09)
Arrythmias			1.04 (0.96 to 1.12)
Cancer			1 (0.95 to 1.05)
Hypothyroidism			1.01 (0.84 to 1.21)
Hyperthyroid			1.01 (0.87 to 1.17)
Pancreatitis			1.08 (0.94 to 1.24)
Binary Treatment Indicator Variables¥			
Anti-hypertensive			0.99 (0.95 to 1.03)
Antiplatelets			1 (0.96 to 1.04)
Anticoagulants			1.05 (0.95 to 1.16)
Anti-arrythmic			1.03 (0.83 to 1.26)
Diuretics			0.88 (0.84 to 0.92)
Statins			1.11 (1.07 to 1.16)
Other lipid lowering drugs			1.09 (1.01 to 1.17)
Antidepressants			1.1 (1.05 to 1.15)
Antipsychotics			0.83 (0.74 to 0.93)
Antiobesity			0.93 (0.82 to 1.05)
Steroids –oral/iv			0.97 (0.9 to 1.05)
Thyroxine			0.97 (0.81 to 1.16)
Anti-thyroid drugs			1.09 (0.67 to 1.79)
Anxiolytics			0.96 (0.89 to 1.03)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 10A3 Cox regression analysis for time to first recording of a HbA1c > 58 mmol/mol for individuals aged ≥ 18 years that intensified treatment only

	Unadjusted (HR, 95% CI)	**Adjusted for Sex & Age (HR, 95% CI)**	**Fully Adjusted Multivariate (HR, 95% CI)**
Treatment			
Sulphonylurea	Ref	Ref	Ref
Sitagliptin	**0.89 (0.82 to 0.96)**	**0.89 (0.82 to 0.96)**	**0.90 (0.82 to 0.98)**
Additional Covariates			
Age at index date (years)		1 (0.99 to 1)	1 (1 to 1)
Sex			
Male		Ref	Ref
Female		1.09 (1.02 to 1.16)	1.09 (1.02 to 1.18)
Baseline HbA1c (mmol/mol)			1.01 (1 to 1.01)
Baseline Weight (kg)			1 (1 to 1)
F2FC*			1 (0.99 to 1.01)
Year Entry			
2007			Ref
2008			0.9 (0.78 to 1.03)
2009			0.92 (0.81 to 1.05)
2010			0.98 (0.86 to 1.12)
2011			0.99 (0.86 to 1.14)
2012			1.07 (0.92 to 1.24)
2013			1.09 (0.92 to 1.29)
2014			1.57 (1.14 to 2.17)
Smoker			
Non			Ref
Ex			1.02 (0.94 to 1.11)
Current			1.04 (0.96 to 1.13)
CKD Stage			
(CrCl>60 ml/min)			Ref
(CrCl 30-59 ml/min)			0.9 (0.81 to 1.02)
(CrCl<30 ml/min)			0.2 (0.03 to 1.41)
Binary Comorbidity Indicator Variables			
Hypoglycaemias			0.99 (0.66 to 1.49)
Excessive Alcohol Intake**			0.93 (0.84 to 1.03)
Heart failure			1.06 (0.93 to 1.2)
Binary Treatment Indicator Variables¥			
Diuretics			0.98 (0.9 to 1.08)
Antidepressants			1.07 (0.99 to 1.17)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 10A4 Cox regression analysis for time to first recording of a HbA1c > 58 mmol/mol for individuals aged ≥ 18 years that switched treatment only

	Unadjusted (HR, 95% CI)	**Adjusted for Sex & Age (HR, 95% CI)**	**Fully Adjusted Multivariate (HR, 95% CI)**
Treatment			
Sulphonylurea	Ref	Ref	Ref
Sitagliptin	**1.14 (1.05 to 1.24)**	**1.13 (1.04 to 1.23)**	**1.17 (1.07 to 1.28)**
Additional Covariates			
Age at index date (years)		0.99 (0.99 to 1)	1 (1 to 1)
Sex			
Male		Ref	Ref
Female		1.05 (0.97 to 1.13)	1.09 (1 to 1.18)
Baseline HbA1c (mmol/mol)			1.01 (1.01 to 1.01)
Baseline Weight (kg)			1 (1 to 1.01)
F2FC*			1 (1 to 1.01)
Year Entry			
2007			Ref
2008			1.04 (0.88 to 1.23)
2009			0.97 (0.83 to 1.14)
2010			0.98 (0.84 to 1.14)
2011			1.06 (0.9 to 1.25)
2012			1 (0.85 to 1.17)
2013			1.04 (0.87 to 1.24)
2014			1.52 (1.18 to 1.96)
Smoker			
Non			Ref
Ex			1.03 (0.94 to 1.13)
Current			1.09 (0.99 to 1.2)
CKD Stage			
(CrCl>60 ml/min)			Ref
(CrCl 30-59 ml/min)			0.92 (0.82 to 1.04)
(CrCl<30 ml/min)			1.48 (0.73 to 3.01)
Binary Comorbidity Indicator Variables			
Hypoglycaemias			1.27 (0.89 to 1.82)
Excessive Alcohol Intake**			0.91 (0.81 to 1.02)
Heart failure			0.96 (0.83 to 1.11)
Binary Treatment Indicator Variables¥			
Diuretics			0.92 (0.83 to 1.02)
Antidepressants			1.09 (0.99 to 1.2)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 10A5 Cox regression analysis for time to first recording of a HbA1c > 58 mmol/mol for individuals aged ≥ 18 "adherent" to medication

	Unadjusted (HR, 95% CI)	**Adjusted for Sex & Age (HR, 95% CI)**	**Fully Adjusted Multivariate (HR, 95% CI)**
Treatment			
Sulphonylurea	Ref	Ref	Ref
Sitagliptin	**0.99 (0.91 to 1.08)**	**0.93 (0.86 to 1.02)**	**0.97 (0.89 to 1.06)**
Additional Covariates			
Age at index date (years)		0.98 (0.97 to 0.98)	0.98 (0.98 to 0.99)
Sex			
Male		Ref	Ref
Female		1.09 (1.02 to 1.15)	1.16 (1.08 to 1.24)
Baseline HbA1c (mmol/mol)			1.02 (1.02 to 1.02)
Baseline Weight (kg)			1 (1 to 1.01)
F2FC*			1.01 (1.01 to 1.02)
Year Entry			
2007			Ref
2008			1.05 (0.94 to 1.17)
2009			0.98 (0.88 to 1.09)
2010			1 (0.9 to 1.12)
2011			1.12 (1 to 1.25)
2012			1.05 (0.93 to 1.2)
2013			0 (0 to 0)
2014			0 (0 to 0)
Smoker			
Non			Ref
Ex			1.04 (0.97 to 1.12)
Current			1.07 (0.99 to 1.16)
CKD Stage			
(CrCl>60 ml/min)			Ref
(CrCl 30-59 ml/min)			0.87 (0.79 to 0.96)
(CrCl<30 ml/min)			0.94 (0.35 to 2.52)
Binary Comorbidity Indicator Variables			
Hypoglycaemias			1.27 (0.89 to 1.82)
Excessive Alcohol Intake**			0.95 (0.87 to 1.04)
Heart failure			1.17 (1.05 to 1.31)
Binary Treatment Indicator Variables¥			
Diuretics			0.84 (0.78 to 0.91)
Antidepressants			1.13 (1.04 to 1.23)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 10A6 Cox regression analysis for time to first recording of a treatment change for individuals aged 18-75 years using parsimonious model

	Unadjusted (HR, 95% CI)	Adjusted for Sex & Age (HR, 95% CI)	Fully Adjusted Multivariable (HR, 95% CI)
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**1.84 (1.74 to 1.95)**	**1.77 (1.67 to 1.87)**	**1.98 (1.86 to 2.1)**
Additional Covariates			
Age at index date (years)		0.97 (0.97 to 0.97)	0.98 (0.98 to 0.98)
Sex			
Male		Ref	Ref
Female		1.22 (1.16 to 1.28)	1.25 (1.18 to 1.32)
Baseline HbA1c (mmol/mol)			1.02 (1.01 to 1.02)
Baseline Weight (kg)			1 (1 to 1)
F2FC*			1.02 (1.02 to 1.03)
Year Entry			
2007			Ref
2008			1.06 (0.96 to 1.18)
2009			1.13 (1.03 to 1.25)
2010			1.03 (0.93 to 1.14)
2011			0.95 (0.85 to 1.05)
2012			0.89 (0.8 to 0.99)
2013			0.93 (0.83 to 1.05)
2014			1.03 (0.86 to 1.25)
Smoker			
Non			Ref
Ex			1.08 (1.02 to 1.15)
Current			1.13 (1.07 to 1.2)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			1.05 (0.99 to 1.12)
Binary Comorbidity Indicator Variables			
Heart failure			1.16 (1.05 to 1.28)
Pancreatitis			1.19 (0.98 to 1.44)
Binary Treatment Indicator Variables¥			
Anticoagulants			1.11 (0.96 to 1.27)
Diuretics			0.92 (0.86 to 0.98)
Other lipid lowering drugs			1.14 (1.03 to 1.27)
Antidepressants			1.17 (1.1 to 1.25)
Antiobesity			1.2 (1.03 to 1.4)

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CI=confidence Interval.

Supplementary Table 10A7 Cox regression analysis for time to first recording of a treatment change for individuals aged 18-75 years using clinical model (based on Direct Acyclic Graph)

	Unadjusted (HR, 95% CI)	**Adjusted for Sex & Age (HR, 95% CI)**	**Fully Adjusted Multivariable (HR, 95% CI)**
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**1.84 (1.74 to 1.95)**	**1.77 (1.67 to 1.87)**	**1.99 (1.87 to 2.12)**
Additional Covariates			
Age at index date (years)		0.97 (0.97 to 0.97)	1.02 (1.01 to 1.02)
Sex			
Male		Ref	
Female		1.22 (1.16 to 1.28)	Ref
Baseline HbA1c (mmol/mol)			1.23 (1.16 to 1.3)
Baseline Weight (kg)			1 (1 to 1)
Year Entry			
2007			1 (0 to 0)
2008			1.07 (0.96 to 1.19)
2009			1.15 (1.04 to 1.27)
2010			1.04 (0.94 to 1.15)
2011			0.95 (0.86 to 1.06)
2012			0.89 (0.8 to 0.99)
2013			0.93 (0.82 to 1.05)
2014			1.06 (0.88 to 1.29)
F2FC*			1.02 (1.02 to 1.03)
Townsend Quintile			
1			Ref
2			1.03 (0.95 to 1.11)
3			1.01 (0.93 to 1.09)
4			1.03 (0.95 to 1.11)
5			1 (0.92 to 1.09)
Smoker			
Non			Ref
Ex			1.08 (1.01 to 1.15)
Current			1.13 (1.06 to 1.21)
CKD Stage			
(CrCl>60 ml/min)			Ref
(CrCl 30-59 ml/min)			0.96 (0.88 to 1.05)
(CrCl<30 ml/min)			0.89 (0.13 to 6.33)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			1.05 (0.99 to 1.12)
Binary Comorbidity Indicator Variables			
Excessive Alcohol Intake**			0.9 (0.84 to 0.97)
History of Hypoglycaemia			1.13 (0.87 to 1.47)
Neuropathy			1.04 (0.9 to 1.19)
Retinopathy			1 (0.93 to 1.08)
Cardiovascular disease			1.07 (1.01 to 1.15)

	Unadjusted (HR, 95% CI)	Adjusted for Sex & Age (HR, 95% CI)	Fully Adjusted Multivariable (HR, 95% CI)
Heart failure			1.14 (1.03 to 1.27)
Anaemias			0.95 (0.87 to 1.05)
Dementia			1.08 (0.66 to 1.76)
Liver disease			1.06 (0.94 to 1.21)
Arrythmias			1.04 (0.91 to 1.18)
Cancer			1.02 (0.94 to 1.1)
Hypothyroidism			0.96 (0.71 to 1.29)
Hyperthyroid			1.02 (0.8 to 1.28)
Pancreatitis			1.22 (1 to 1.48)
Binary Treatment Indicator Variables¥			
Anti-hypertensive			0.91 (0.86 to 0.97)
Antiplatelets			1.02 (0.96 to 1.08)
Anticoagulants			1.06 (0.9 to 1.24)
Anti-arrythmic			1.19 (0.87 to 1.63)
Diuretics			0.95 (0.88 to 1.02)
Statins			1.03 (0.97 to 1.09)
Other lipid lowering drugs			1.13 (1.02 to 1.26)
Antidepressants			1.17 (1.1 to 1.25)
Antipsychotics			0.89 (0.76 to 1.05)
Antiobesity			1.17 (1 to 1.37)
Steroids –oral/iv			0.97 (0.85 to 1.1)
Thyroxine			1.11 (0.82 to 1.49)
Anti-thyroid drugs			0.78 (0.34 to 1.79)
Anxiolytics			0.96 (0.85 to 1.08)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 10A8 Cox regression analysis for time to first recording of a treatment change for individuals aged 18-75 years that intensified treatment only

	Unadjusted (HR, 95% CI)	Adjusted for Sex & Age (HR, 95% CI)	Fully Adjusted Multivariable (HR, 95% CI)
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**1.44 (1.34 to 1.56)**	**1.44 (1.33 to 1.55)**	**1.36 (1.25 to 1.48)**
Additional Covariates			
Age at index date (years)		0.99 (0.99 to 1)	0.99 (0.99 to 1)
Sex			
Male		Ref	Ref
Female		1.06 (0.99 to 1.14)	1.07 (1 to 1.15)
Baseline HbA1c (mmol/mol)			1.01 (1.01 to 1.01)
Baseline Weight (kg)			1 (1 to 1)
F2FC*			1.01 (1 to 1.02)
Year Entry			
2007			Ref
2008			1.18 (1.03 to 1.35)
2009			1.22 (1.07 to 1.39)
2010			1.36 (1.19 to 1.55)
2011			1.27 (1.11 to 1.45)
2012			1.32 (1.15 to 1.53)
2013			2.94 (2.48 to 3.49)
2014			8.33 (6.14 to 11.29)
Smoker			
Non			Ref
Ex			1 (0.92 to 1.08)
Current			1.06 (0.98 to 1.15)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			0.96 (0.89 to 1.04)
Binary Comorbidity Indicator Variables			
Heart failure			1.15 (1.01 to 1.31)
Pancreatitis			1.06 (0.81 to 1.37)
Binary Treatment Indicator Variables¥			
Anticoagulants			0.9 (0.75 to 1.08)
Diuretics			1.01 (0.93 to 1.1)
Other lipid lowering drugs			1.05 (0.92 to 1.21)
Antidepressants			1.04 (0.96 to 1.13)
Antiobesity			0.98 (0.79 to 1.23)

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CI=confidence Interval.

Supplementary Table 10A9 Cox regression analysis for time to first recording of a treatment change for individuals aged 18-75 years that switched treatment only

	Unadjusted (HR, 95% CI)	**Adjusted for Sex & Age (HR, 95% CI)**	**Fully Adjusted Multivariable (HR, 95% CI)**
Treatment			
Sulphonylurea	Ref	Ref	Ref
Sitagliptin	**1.11 (1.02 to 1.2)**	**1.1 (1.02 to 1.19)**	**1.08 (0.99 to 1.18)**
Additional Covariates			
Age at index date (years)		1 (0.99 to 1)	0.99 (0.99 to 1)
Sex			
Male		Ref	Ref
Female		1.09 (1.02 to 1.17)	1.11 (1.03 to 1.2)
Baseline HbA1c (mmol/mol)			1.01 (1 to 1.01)
Baseline Weight (kg)			1 (1 to 1)
F2FC*			1.01 (1 to 1.01)
Year Entry			
2007			Ref
2008			0.94 (0.81 to 1.11)
2009			1.04 (0.9 to 1.2)
2010			1.04 (0.9 to 1.21)
2011			1.04 (0.9 to 1.21)
2012			1.14 (0.98 to 1.32)
2013			1.8 (1.53 to 2.12)
2014			2.91 (2.32 to 3.65)
Smoker			
Non			Ref
Ex			1.05 (0.96 to 1.14)
Current			1.01 (0.92 to 1.1)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			0.97 (0.9 to 1.06)
Binary Comorbidity Indicator Variables			
Heart failure			1.13 (0.99 to 1.3)
Pancreatitis			1.06 (0.82 to 1.39)
Binary Treatment Indicator Variables¥			
Anticoagulants			1.05 (0.87 to 1.27)
Diuretics			1.06 (0.96 to 1.16)
Other lipid lowering drugs			0.98 (0.84 to 1.14)
Antidepressants			1.08 (0.98 to 1.18)
Antiobesity			1.04 (0.84 to 1.29)

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CI=confidence Interval.

Supplementary Table 10A10 Cox regression analysis for time to first recording of a treatment change for individuals aged 18-75 "adherent" to medication

	Unadjusted (HR, 95% CI)	**Adjusted for Sex, Age (HR, 95% CI)**	**Fully Adjusted Multivariable (HR, 95% CI)**
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**1.95 (1.74 to 2.2)**	**1.88 (1.67 to 2.11)**	**2.16 (1.9 to 2.45)**
Additional Covariates			
Age at index date (years)		0.97 (0.97 to 0.98)	0.98 (0.97 to 0.98)
Sex			
Male		Ref	Ref
Female		1.03 (0.93 to 1.14)	1.09 (0.98 to 1.22)
Baseline HbA1c (mmol/mol)			1.02 (1.02 to 1.02)
Baseline Weight (kg)			1.01 (1 to 1.01)
F2FC*			1.02 (1.01 to 1.03)
Year Entry			
2007			Ref
2008			1.27 (1.05 to 1.54)
2009			1.14 (0.94 to 1.38)
2010			1.04 (0.86 to 1.26)
2011			1.07 (0.88 to 1.3)
2012			0.85 (0.68 to 1.07)
Smoker			
Non			Ref
Ex			0.95 (0.84 to 1.07)
Current			1.08 (0.95 to 1.22)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			1.09 (0.96 to 1.24)
Binary Comorbidity Indicator Variables			
Heart failure			1.45 (0.98 to 2.14)
Pancreatitis			1.45 (0.98 to 2.14)
Binary Treatment Indicator Variables¥			
Anticoagulants			1.11 (0.83 to 1.47)
Diuretics			0.99 (0.87 to 1.13)
Other lipid lowering drugs			1.38 (1.14 to 1.68)
Antidepressants			1.08 (0.95 to 1.24)
Antiobesity			1.06 (0.76 to 1.47)

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CI=confidence Interval.

Supplementary Table 10A11 Cox regression analysis for time to first recording of a treatment change for individuals aged ≥75 years using parsimonious model

	Unadjusted (HR, 95% CI)	Adjusted for Sex & Age (HR, 95% CI)	Fully Adjusted Multivariable (HR, 95% CI)
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**2.48 (1.99 to 3.08)**	**2.45 (1.97 to 3.05)**	**2.56 (2.03 to 3.23)**
Additional Covariates			
Age at index date (years)		0.96 (0.94 to 0.99)	0.95 (0.92 to 0.97)
Sex			
Male		Ref	Ref
Female		1.05 (0.87 to 1.26)	1.09 (0.89 to 1.34)
Baseline HbA1c (mmol/mol)			1.02 (1.01 to 1.02)
Baseline Weight (kg)			1 (0.99 to 1)
F2FC*			1.02 (1 to 1.04)
Year Entry			
2007			Ref
2008			1.04 (0.66 to 1.65)
2009			1.59 (1.06 to 2.41)
2010			1.4 (0.93 to 2.12)
2011			1.71 (1.12 to 2.6)
2012			1.78 (1.16 to 2.72)
2013			1.15 (0.7 to 1.88)
2014			2.56 (1.42 to 4.63)
Smoker			
Non			Ref
Ex			0.98 (0.8 to 1.2)
Current			0.79 (0.58 to 1.09)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			1.01 (0.83 to 1.23)
Binary Comorbidity Indicator Variables			
Heart failure			1.39 (1.08 to 1.8)
Pancreatitis			1.35 (0.64 to 2.87)
Binary Treatment Indicator Variables¥			
Anticoagulants			1.05 (0.78 to 1.41)
Diuretics			0.89 (0.72 to 1.11)
Other lipid lowering drugs			0.85 (0.54 to 1.33)
Antidepressants			0.99 (0.75 to 1.29)
Antiobesity			Not Calculable

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CI=confidence Interval.

Supplementary Table 10A12 Cox regression analysis for time to first recording of a treatment change for individuals aged ≥75 years using clinical model (DAG model)

	Unadjusted (HR, 95% CI)	**Adjusted for Sex & Age (HR, 95% CI)**	**Fully Adjusted Multivariable (HR, 95% CI)**
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**2.51 (2.01 to 3.14)**	**2.49 (1.99 to 3.1)**	**2.63 (2.07 to 3.34)**
Additional Covariates			
Age at index date (years)		0.96 (0.94 to 0.99)	1.02 (1.01 to 1.02)
Sex			
Male		Ref	
Female		1.05 (0.87 to 1.26)	Ref
Baseline HbA1c (mmol/mol)			1.09 (0.87 to 1.36)
Baseline Weight (kg)			1 (0.99 to 1.01)
Year Entry			
2007			Ref
2008			1.08 (0.68 to 1.71)
2009			1.59 (1.05 to 2.42)
2010			1.4 (0.92 to 2.13)
2011			1.67 (1.09 to 2.55)
2012			1.78 (1.16 to 2.74)
2013			1.13 (0.68 to 1.88)
2014			2.83 (1.56 to 5.15)
F2FC*			1.02 (1 to 1.04)
Townsend Quintile			
1			Ref
2			0.97 (0.75 to 1.27)
3			1.06 (0.8 to 1.39)
4			0.65 (0.47 to 0.91)
5			1.22 (0.9 to 1.67)
Smoker			
Non			Ref
Ex			0.95 (0.77 to 1.17)
Current			0.74 (0.53 to 1.03)
CKD Stage			
(CrCl>60 ml/min)			Ref
(CrCl 30-59 ml/min)			1.03 (0.84 to 1.27)
(CrCl<30 ml/min)			1.96 (0.97 to 3.99)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			1.01 (0.83 to 1.25)
Binary Comorbidity Indicator Variables			
Excessive Alcohol Intake**			0.95 (0.66 to 1.36)
History of Hypoglycaemia			1.34 (0.49 to 3.68)
Neuropathy			1.41 (1 to 2)
Retinopathy			0.97 (0.76 to 1.25)
Cardiovascular disease			1.04 (0.85 to 1.28)
Heart failure			1.45 (1.1 to 1.92)

	Unadjusted (HR, 95% CI)	Adjusted for Sex & Age (HR, 95% CI)	Fully Adjusted Multivariable (HR, 95% CI)
Anaemias			1.06 (0.8 to 1.41)
Dementia			1.14 (0.63 to 2.05)
Liver disease			1.2 (0.67 to 2.17)
Arrythmias			0.75 (0.53 to 1.04)
Cancer			0.92 (0.74 to 1.15)
Hypothyroidism			1.03 (0.41 to 2.6)
Hyperthyroid			1.18 (0.59 to 2.37)
Pancreatitis			1.36 (0.63 to 2.9)
Binary Treatment Indicator Variables¥			
Anti-hypertensive			0.9 (0.69 to 1.17)
Antiplatelets			1.06 (0.85 to 1.31)
Anticoagulants			1.34 (0.9 to 1.98)
Anti-arrythmic			1.24 (0.54 to 2.87)
Diuretics			0.91 (0.72 to 1.15)
Statins			1 (0.78 to 1.27)
Other lipid lowering drugs			0.78 (0.49 to 1.25)
Antidepressants			0.98 (0.74 to 1.31)
Antipsychotics			0.14 (0.02 to 1.05)
Antiobesity			Not Calculable
Steroids –oral/iv			0.85 (0.61 to 1.19)
Thyroxine			0.96 (0.39 to 2.4)
Anti-thyroid drugs			2.40 (0.31 to 18.28)
Anxiolytics			0.93 (0.61 to 1.41)

*Face to Face Consultation Frequency per year
**Excessive Alcohol Intake is those identified as consuming > 28 units a week if female and >35 units if male
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CrCl=Creatinine Clearance, CI=confidence Interval.

Supplementary Table 10A13 Cox regression analysis for time to first recording of a treatment change for individuals aged ≥75 years that intensified treatment only

	Unadjusted (HR, 95% CI)	Adjusted for Sex & Age (HR, 95% CI)	Fully Adjusted Multivariable (HR, 95% CI)
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**1.67 (1.18 to 2.37)**	**1.66 (1.17 to 2.35)**	**1.61 (1.08 to 2.42)**
Additional Covariates			
Age at index date (years)		1.02 (0.98 to 1.07)	1.03 (0.98 to 1.08)
Sex			
Male		Ref	Ref
Female		0.9 (0.67 to 1.2)	0.73 (0.5 to 1.06)
Baseline HbA1c (mmol/mol)			1.01 (1.01 to 1.02)
Baseline Weight (kg)			0.99 (0.98 to 1)
F2FC*			0.98 (0.95 to 1.01)
Year Entry			
2007			Ref
2008			0.9 (0.42 to 1.94)
2009			1.08 (0.53 to 2.17)
2010			0.92 (0.46 to 1.84)
2011			1.44 (0.68 to 3.01)
2012			1.02 (0.47 to 2.19)
2013			2.7 (1.1 to 6.6)
2014			15.78 (5.02 to 49.57)
Smoker			
Non			Ref
Ex			0.9 (0.62 to 1.3)
Current			1.35 (0.72 to 2.5)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			0.91 (0.65 to 1.29)
Binary Comorbidity Indicator Variables			
Heart failure			1.72 (1.05 to 2.81)
Pancreatitis			7.67 (0.93 to 63.5)
Binary Treatment Indicator Variables¥			
Anticoagulants			0.71 (0.43 to 1.19)
Diuretics			0.71 (0.47 to 1.06)
Other lipid lowering drugs			1.6 (0.6 to 4.3)
Antidepressants			1.42 (0.89 to 2.25)
Antiobesity			Not calculable

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CI=confidence Interval.

Supplementary Table 10A14 Cox regression analysis for time to first recording of a treatment change for individuals aged ≥75 years that switched treatment only

	Unadjusted (HR, 95% CI)	Adjusted for Sex & Age (HR, 95% CI)	Fully Adjusted Multivariable (HR, 95% CI)
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**1.04 (0.78 to 1.39)**	**1.09 (0.82 to 1.46)**	**1.04 (0.76 to 1.43)**
Additional Covariates			
Age at index date (years)		0.96 (0.93 to 0.99)	0.95 (0.92 to 0.98)
Sex			
Male		Ref	Ref
Female		1.11 (0.88 to 1.42)	0.96 (0.72 to 1.27)
Baseline HbA1c (mmol/mol)			1 (1 to 1.01)
Baseline Weight (kg)			0.99 (0.98 to 1)
F2FC*			1 (0.98 to 1.02)
Year Entry			
2007			Ref
2008			0.8 (0.42 to 1.55)
2009			0.67 (0.38 to 1.18)
2010			0.91 (0.53 to 1.57)
2011			0.94 (0.54 to 1.64)
2012			1.03 (0.59 to 1.79)
2013			2.25 (1.18 to 4.29)
2014			3.04 (1.39 to 6.62)
Smoker			
Non			Ref
Ex			1.03 (0.79 to 1.35)
Current			1.21 (0.79 to 1.84)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			1.09 (0.82 to 1.44)
Binary Comorbidity Indicator Variables			
Heart failure			0.98 (0.69 to 1.38)
Pancreatitis			1.02 (0.44 to 2.4)
Binary Treatment Indicator Variables¥			
Anticoagulants			1.02 (0.66 to 1.57)
Diuretics			1.31 (0.96 to 1.79)
Other lipid lowering drugs			1.17 (0.66 to 2.09)
Antidepressants			0.86 (0.57 to 1.3)
Antiobesity			Not Calculable

*Face to Face Consultation Frequency per year
¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CI=confidence Interval.

Supplementary Table 10A15 Cox regression analysis for time to first recording of a treatment change for individuals aged ≥75 "adherent" to medication

	Unadjusted (95% CI)	Adjusted for Sex, Age (HR, 95% CI)	Fully Adjusted Multivariate (95% CI)
Treatment			
Sulphonylurea	**Ref**	**Ref**	**Ref**
Sitagliptin	**2.29 (1.4 to 3.76)**	**2.26 (1.38 to 3.71)**	**2.44 (1.45 to 4.1)**
Additional Covariates			
Age at index date (years)		0.95 (0.89 to 1.01)	0.95 (0.89 to 1.02)
Sex			
Male		Ref	Ref
Female		0.87 (0.57 to 1.31)	1.17 (0.73 to 1.87)
Baseline HbA1c (mmol/mol)			1.03 (1.02 to 1.03)
Baseline Weight (kg)			1.01 (0.99 to 1.02)
F2FC*			1.04 (1 to 1.08)
Year Entry			
2007			Ref
2008			2.78 (1.02 to 7.58)
2009			3.12 (1.18 to 8.21)
2010			2.51 (0.95 to 6.69)
2011			2.23 (0.81 to 6.16)
2012			1.41 (0.4 to 4.94)
Smoker			
Non			Ref
Ex			1.22 (0.77 to 1.91)
Current			0.92 (0.45 to 1.87)
Metformin Dose at Baseline			
<1500mg			Ref
≥1500mg			1.33 (0.82 to 2.15)
Binary Comorbidity Indicator Variables			
Heart failure			0.88 (0.48 to 1.63)
Pancreatitis			Not Calculable
Binary Treatment Indicator Variables¥			
Anticoagulants			1.5 (0.76 to 2.97)
Diuretics			0.76 (0.47 to 1.25)
Other lipid lowering drugs			Not Calculable
Antidepressants			1.31 (0.72 to 2.37)
Antiobesity			Not Calculable

* Face to Face Consultation Frequency per year ¥Concomitantly prescribed within 3 months before index date
HR=Hazard Ratio, CrCl=Creatinine Clearance, CI=confidence Interval.

Appendix H. **Manuscripts published based on work completed during Thesis**

1. Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. BMJ Open 2016; 6(1): e010210. Available via http://bmjopen.bmj.com/content/6/1/e010210

2. Sharma M, Petersen I, Nazareth I, Coton SJ. An algorithm for identification and classification of individuals with type 1 and type 2 diabetes mellitus in a large primary care database. Clin Epidemiol 2016; 8:373-80. Available via https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5066690/pdf/clep-8-373.pdf

3. Sharma M, Beckley N, Nazareth I, Petersen I. Effectiveness of sitagliptin compared to sulfonylureas for type 2 diabetes mellitus inadequately controlled on metformin: a systematic review and meta-analysis. BMJ Open 2017; 7(10):e017260 Available via http://bmjopen.bmj.com/content/bmjopen/7/10/e017260.full.pdf

BMJ Open

Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study

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ABSTRACT

Objective: To investigate trends in incident and prevalent diagnoses of type 2 diabetes mellitus (T2DM) and its pharmacological treatment between 2000 and 2013.

Design: Analysis of longitudinal electronic health records in The Health Improvement Network (THIN) primary care database.

Setting: UK primary care.

Participants: In total, we examined 8 838 031 individuals aged 0–99 years.

Outcome measures: The incidence and prevalence of T2DM between 2000 and 2013, and the effect of age, sex and social deprivation on these measures were examined. Changes in prescribing patterns of antidiabetic therapy between 2000 and 2013 were also investigated.

Results: Overall, 406 344 individuals had a diagnosis of T2DM, of which 203 639 were newly diagnosed between 2000 and 2013. The incidence of T2DM rose from 3.69 per 1000 person-years at risk (PYAR) (95% CI 3.58 to 3.81) in 2000 to 3.99 per 1000 PYAR (95% CI 3.90 to 4.08) in 2013 among men; and from 3.06 per 1000 PYAR (95% CI 2.95 to 3.17) to 3.73 per 1000 PYAR (95% CI 3.65 to 3.82) among women. Prevalence of T2DM more than doubled from 2.39% (95% CI 2.37 to 2.41) in 2000 to 5.32% (95% CI 5.30 to 5.34) in 2013. Being male, older, and from a more socially deprived area was strongly associated with having T2DM, ($p<0.001$). Prescribing changes over time reflected emerging clinical guidance and novel treatments. In 2013, metformin prescribing peaked at 83.6% (95% CI 83.4% to 83.8%), while sulfonylureas prescribing reached a low of 41.4% (95% CI 41.1% to 41.7%). Both remained, however, the most commonly used pharmacological treatments as first-line agents and add-on therapy. Thiazolidinediones and incretin based therapies (gliptins and GLP-1 analogues) were also prescribed as alternate add-on therapy options, however were rarely used for first-line treatment in T2DM.

Conclusions: Prevalent cases of T2DM more than doubled between 2000 and 2013, while the number of incident cases increased more steadily. Changes in prescribing patterns observed may reflect the impact of national policies and prescribing guidelines on UK primary care.

Strengths and limitations of this study

- This is, to the best of our knowledge, the first study to examine both changes in rates of incident and prevalent diagnosis of type 2 diabetes mellitus and antidiabetic prescribing patterns using 'real world' UK primary care data between 2000 and 2013.
- This study does not contain data from secondary care; however, type 2 diabetes mellitus is largely managed in the primary care setting.
- Although several explanations for the factors that might have triggered changes in prescribing patterns of antidiabetic medications over time are provided, there is no means of determining the exact rationale behind prescribing decisions without gathering more detailed information on prescribing for each therapeutic category.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is an increasing public health burden, and managing the disease and its complications accounts for close to 10% of the entire National Health Service (NHS) budget in the UK.[1] T2DM was historically managed in hospitals, but there has been a gradual shift towards primary care. The NHS quality and outcomes framework (QOF), introduced as part of the general practitioner (GP) contract in 2004, offers several financial incentives to encourage better monitoring and management of several diseases in primary care, including diabetes.[2] Hence, primary care data from the UK is increasingly being used to study the disease and its management.[3 4]

Significant developments over the past decade have influenced both the diagnosis and pharmacological treatment of T2DM in the UK. In 2000, for example, implementation of the revised WHO diabetes diagnostic criteria led to a lower fasting plasma glucose

threshold of 7.0 mmol/L being used for diagnosis rather than 7.8 mmol/L.[5] There has also been a greater awareness of the need for aggressive treatment of T2DM to reduce and delay long-term complications such as cardiovascular and renal disease.[6]

Several new therapies have emerged in the past decade, such as incretin-based therapies and SGLT-2 inhibitors, making the choice of suitable antidiabetic regimens challenging.[7] This may partly explain the inertia in intensifying treatment for T2DM.[8] Periodic guidance from national and international bodies, such as National Institute of Health and Care Excellence (NICE), American Diabetes Association (ADA) and European Association of Diabetics (EASD), in particular, have offered more objective advice to prescribers.[9 10]

Our aim was to investigate how the incidence and prevalence of T2DM diagnoses as well as prescribing patterns have changed between 2000 and 2013 using data from The Health Improvement Network (THIN) primary care database.

METHODS

Data source

THIN is one of the largest databases to collect information on patient demographics, disease diagnosis, management and prescribing from UK primary care. THIN contains anonymised medical records from over 550 general practices throughout the UK, with around 12 million patients contributing data. It is reasonably representative of the UK population.[11 12] Information is collected during routine patient consultations with GPs from when a patient registers at a THIN affiliated general practice. Symptoms and diagnosis of disease are recorded using the Read code, hierarchical coding system.[13 14] THIN also provides information on referrals made to secondary care and anonymised free text information. A measure of social deprivation recorded as quintiles of Townsend scores is also provided.[15]

Study population and period

All data included in this study was from practices which met the acceptable mortality reporting (AMR) and acceptable computer usage (ACU) standards. These are measures of quality assurance for THIN data.[16 17] The AMR date is the date after which the practice is confirmed to have a rate of mortality sufficiently similar to that expected for a practice with its demographic characteristics, based on data from the Office for National Statistics.[16] The ACU date is the date after which the practice is confirmed to have on average at least one medical record, one additional health record and two prescriptions per patient per year.[17] We included all individuals aged 0–99 years who were registered with a general practice contributing data between 2000 and 2013.

The recording of diabetes diagnoses and management in THIN is comprehensive and hence, there are several ways an individual may be identified as diabetic. We developed an algorithm to identify individuals with diabetes mellitus on whether they had at least two of the following records: (1) a diagnostic code for diabetes, (2) supporting evidence of diabetes, for example, screening for diabetic retinopathy or (3) treatment for diabetes. The first record of any of these three was considered as the date of diagnosis. As some Read codes are non-specific, we sought to distinguish patients with diabetes as type 2 based on age at diagnosis, types of treatment and timing of the diabetes diagnosis.[18] For example, patients with diabetes aged ≥35 years at time of diagnosis, on non-insulin antidiabetic treatment or being managed without treatment were classified as type 2. Patients with diabetes diagnosed <35 years of age and on insulin were classified as type 1. A sample of 500 complete electronic healthcare records for individuals with diabetes were reviewed manually in THIN to assess if our clinical classification algorithm for diabetes type based on parameters above had identified diabetes type correctly. In all 500 cases, manual assignment of diabetes type based on clinical assessment of the entire record and algorithmic assignment led to equivalent classification.

Definition of main outcomes

Incidence of T2DM

The date at which the first recording of T2DM was made was classified as the index date for diagnosis. Therefore, our use of the term incidence with respect to T2DM in this study refers to the first record of T2DM to appear in a patient's electronic primary care record in the THIN database. We excluded those who had their first recording of T2DM made within the first 9 months of practice registration as these were more likely to be prevalent cases.[19] We accounted for deaths and patients who had left the practices in our denominator (follow-up time).

Prevalence of T2DM

For our analysis on prevalence of T2DM, we included as our numerator all individuals who were first recorded as having T2DM within our study period and those recorded as having T2DM from previous years. The denominator included all individuals registered with a general practice between 2000 and 2013. We accounted for deaths and patients who had left the practices.

Prescription patterns analysis

The prevalence of use of different antidiabetic medicines for T2DM was also compared across the time period 2000–2013. We grouped antidiabetic medications by therapeutic class into nine categories: metformin, sulfonylureas, insulins, thiazolidinediones, gliptins, GLP-1 analogues, SGLT-2 inhibitors, meglitinides and acarbose. Prevalence of prescribed medications was calculated by dividing the total number of individuals issued a prescription for a particular antidiabetic medication class by the total number of individuals issued any antidiabetic medication in that calendar year.

Patients with an incident recording of T2DM between 2000 and 2013 were analysed to examine how prescribing habits may have changed over time for newly diagnosed T2DM specifically. We determined what antidiabetic drug was prescribed for initiating treatment in T2DM, and then examined what antidiabetic agents were typically added on by prescribers at a later stage (when the disease had progressed further).

Statistical analyses

The overall crude incidence of T2DM was estimated per 1000 person years at risk (PYAR). This was determined by totalling the number of patients with a first recording of T2DM between 2000 and 2013, and then dividing this number by the total person years of follow-up for all patient records for this period. We also determined crude incidence rates by age, gender, social deprivation (Townsend Score), and calendar year by restricting the person years of follow-up to the respective category in question. Person time was measured from the latest of: the date of general practice registration plus 9 months or 1 January 2000 to the earliest of: date of first recording of T2DM, date of death, date patient left the practice, last date of data collection from that practice or 31 December 2013. Multivariable Poisson regression analysis with (log) person time as an offset was used to analyse changes in incidence by age, gender, social deprivation and calendar year while controlling for the other respective variables.

The overall crude prevalence of T2DM was calculated by dividing the total number of patients with T2DM by the total number of GP-registered patients between 2000 and 2013 accounting for deaths and patients who had left the practices. Crude prevalence by age, gender, social deprivation and calendar year was also determined. Multivariable Poisson regression analysis was used to analyse changes in prevalence of T2DM and also the effect of age, gender, social deprivation and calendar year while controlling for the other respective variables.

To investigate the impact of clustering by practice, multilevel random intercept models were compared to all our standard Poisson models. Likelihood ratio tests were used to explore the significance of interaction between variables.

Prescription records were also analysed to describe changes over time in prescribing habits in primary care. The percentage of patients with T2DM prescribed different antidiabetic therapies for ever-use (prevalence), first-line use and as add-on therapy was determined for each calendar year and the CIs were calculated.

Stata (Version 13.1) was used to conduct all analyses.

Ethics

THIN has been used for scientific research since approval from the NHS South-East Multi-Centre Research Ethics Committee in 2003. Scientific approval to undertake this study was obtained from CMD Medical Research's Scientific Review Committee in February 2015. (SRC Reference Number: 15-011).

RESULTS

In total, 406 344 individuals with T2DM were identified and among these, 203 639 were newly diagnosed between 2000 and 2013.

Incidence of T2DM

The incidence of T2DM increased from 3.69 per 1000 PYAR (95% CI 3.58 to 3.81) in 2000 to 3.99 per 1000 PYAR (95% CI 3.90 to 4.08) in 2013 for men; and from 3.06 per 1000 PYAR (95% CI 2.95 to 3.17) to 3.73 per 1000 PYAR (95% CI 3.65 to 3.82) in 2013 for women (table 1 and online supplementary appendix 1). Incidence peaked in 2004 for both men and women: 4.80 per 1000 PYAR (95% CI 4.70 to 4.90) and 4.28 per 1000 PYAR (95% CI 4.19 to 4.38), respectively. There was a significant interaction between age and gender ($p<0.001$); hence, all results are presented separately for men and women in table 1. Women had a lower incidence of T2DM than men (incidence rate ratios (adjusted) 0.81 (95% CI 0.80 to 0.82) and individuals from the most socially deprived areas had a significantly higher incidence than individuals from the least deprived areas (Townsend Quintile 5 vs Townsend Quintile 1; (IRR 1.57 95% CI 1.54 to 1.60) for men and (IRR 1.92 95% CI 1.88 to 1.97) for women). In general, incidence of T2DM increased with age, peaking between 70 and 79 years. Between ages 10 and 40 years, the incidence of T2DM was higher among women. However, after the age of 40 years, the crude incident rate became higher among men though adjusted incidence rates were similar.

Prevalence of T2DM

The prevalence of T2DM more than doubled from 2.39% (95% CI 2.37% to 2.41%) in 2000 to 5.32% (95% CI 5.30% to 5.34%) in 2013 (table 2 and online supplementary appendix 2). Prevalence was lower among women (IRR 0.77, 95% CI 0.77 to 0.77) and highest among individuals in the most deprived areas (Townsend quintile 5 vs Townsend quintile 1; (IRR 1.75, 95% CI 1.74 to 1.75)). The prevalence increased with age. The highest crude percentage of patients with T2DM was seen in the 60–69 years age band: 37.65% (95% CI 37.50% to 37.79%). However, the highest adjusted prevalence was seen among the 70–79 years age band (70–79 years age band vs 40–49 years age band (IRR 5.95, 95% CI 5.92 to 5.97)) (table 2).

Prescribing in T2DM

Prevalence of antidiabetic medicine prescribed in patients with T2DM

A total of 305 765 (75.2%) patients of 406 344 with T2DM were prescribed antidiabetic medication. The prescribing of metformin rose from 55.4% (95% CI 55.0% to 55.8%) in 2000 to 83.6% (95% CI 83.4% to 83.8%) in 2013, while the prescribing of sulfonylureas decreased from 64.8% (95% CI 64.3% to 65.2%) in 2000 to 41.4% (95% CI 41.1% to 41.7%) of treated

Table 1 Incidence of type 2 diabetes mellitus by sociodemographic factors and year

	Incidence of type 2 diabetes			
	Rate per 1000 PYAR (95% CI)		Adjusted IRR (95% CI)*	
	Men	Women	Men	Women
Overall	4.19 (4.17 to 4.21)	3.72 (3.70 to 3.74)	1	0.81 (0.80 to 0.82)
Age, years				
0–9	0.04 (0.03 to 0.05)	0.04 (0.04 to 0.05)	0.01 (0.01 to 0.01)	0.01 (0.01 to 0.02)
10–19	0.11 (0.10 to 0.13)	0.28 (0.26 to 0.30)	0.03 (0.03 to 0.03)	0.09 (0.09 to 0.10)
20–29	0.36 (0.34 to 0.38)	1.15 (1.11 to 1.19)	0.09 (0.08 to 0.09)	0.37 (0.35 to 0.38)
30–39	1.36 (1.32 to 1.39)	1.91 (1.86 to 1.95)	0.33 (0.32 to 0.34)	0.63 (0.61 to 0.65)
40–49	4.02 (3.97 to 4.08)	3.00 (2.95 to 3.05)	1	1
50–59	7.86 (7.78 to 7.95)	5.43 (5.36 to 5.50)	1.98 (1.94 to 2.01)	1.83 (1.79 to 1.87)
60–69	11.87 (11.74 to 12.00)	8.48 (8.38 to 8.59)	2.98 (2.92 to 3.03)	2.84 (2.78 to 2.90)
70–79	12.68 (12.51 to 12.85)	10.32 (10.19 to 10.46)	3.18 (3.12 to 3.25)	3.43 (3.35 to 3.50)
80–89	9.08 (8.87 to 9.30)	8.00 (7.84 to 8.15)	2.26 (2.19 to 2.32)	2.57 (2.50 to 2.64)
90–99	5.96 (5.49 to 6.46)	4.55 (4.31 to 4.81)	1.48 (1.36 to 1.61)	1.45 (1.37 to 1.54)
Townsend quintile				
1	3.86 (3.82 to 3.91)	2.99 (2.95 to 3.03)	1	1
2	4.19 (4.14 to 4.25)	3.50 (3.46 to 3.55)	1.09 (1.07 to 1.11)	1.15 (1.13 to 1.17)
3	4.29 (4.24 to 4.34)	3.86 (3.81 to 3.91)	1.25 (1.23 to 1.27)	1.37 (1.35 to 1.40)
4	4.47 (4.41 to 4.53)	4.32 (4.26 to 4.38)	1.42 (1.40 to 1.45)	1.63 (1.60 to 1.66)
5	4.62 (4.55 to 4.70)	4.75 (4.68 to 4.83)	1.57 (1.54 to 1.60)	1.92 (1.88 to 1.97)
Year				
2000	3.69 (3.58 to 3.81)	3.06 (2.95 to 3.17)	1	1
2001	4.20 (4.08 to 4.31)	3.52 (3.42 to 3.63)	1.14 (1.09 to 1.19)	1.16 (1.10 to 1.21)
2002	4.48 (4.37 to 4.59)	3.73 (3.63 to 3.83)	1.22 (1.17 to 1.27)	1.24 (1.18 to 1.29)
2003	4.52 (4.41 to 4.62)	3.96 (3.87 to 4.06)	1.24 (1.19 to 1.29)	1.32 (1.27 to 1.38)
2004	4.80 (4.70 to 4.90)	4.28 (4.19 to 4.38)	1.32 (1.27 to 1.37)	1.44 (1.38 to 1.50)
2005	4.56 (4.46 to 4.66)	4.04 (3.95 to 4.13)	1.25 (1.20 to 1.30)	1.36 (1.30 to 1.42)
2006	4.52 (4.42 to 4.61)	3.93 (3.84 to 4.02)	1.24 (1.19 to 1.29)	1.33 (1.27 to 1.39)
2007	4.62 (4.52 to 4.72)	4.07 (3.98 to 4.16)	1.26 (1.22 to 1.31)	1.37 (1.32 to 1.43)
2008	4.62 (4.52 to 4.71)	4.06 (3.97 to 4.15)	1.26 (1.21 to 1.31)	1.37 (1.32 to 1.43)
2009	4.71 (4.61 to 4.80)	4.26 (4.18 to 4.36)	1.29 (1.24 to 1.34)	1.45 (1.39 to 1.51)
2010	4.48 (4.39 to 4.58)	4.10 (4.01 to 4.19)	1.23 (1.18 to 1.28)	1.40 (1.34 to 1.46)
2011	4.26 (4.17 to 4.35)	3.97 (3.88 to 4.05)	1.16 (1.12 to 1.21)	1.35 (1.30 to 1.41)
2012	4.40 (4.31 to 4.49)	4.00 (3.91 to 4.09)	1.20 (1.16 to 1.25)	1.37 (1.31 to 1.43)
2013	3.99 (3.90 to 4.08)	3.73 (3.65 to 3.82)	1.09 (1.05 to 1.13)	1.28 (1.22 to 1.33)

*Adjusted for other variables considered; age band, Townsend quintile, calendar year, respectively.
†Table 1 above is presented stratified by gender due to significant age-gender interaction (p<0.001).
‡For figure displaying data above, please consult online supplementary appendix 1.

patients with T2DM by 2013 (figure 1 and online supplementary appendix 3).

Prescribing of thiazolidinediones peaked in 2007 at 16.0% (95% CI 15.8% to 16.3%), while that of gliptins peaked in 2013 at 15.4% (95% CI 15.2% to 15.7%) of all treated patients (figure 1). Prescribing of acarbose and meglitinides declined and were prescribed in <0.5% of patients with T2DM on antidiabetic medications by 2013. Prescribing of insulin, however, remained stable with 20–24% of treated patients being annually prescribed insulin between 2000 and 2013.

Medicines used to initiate treatment in newly diagnosed patients with T2DM

A total of 127 523 (62.6%) of 203 639 newly diagnosed patients with T2DM were initiated on treatment between 2000 and 2013. In 2000, 51.1% (95% CI 49.2% to 53.0%) were initiated on sulfonylureas and 45.1% (95% CI 43.2% to 47.1%) on metformin (figure 2 and online supplementary appendix 4). Use of metformin as first-line therapy increased annually and by 2013, 91.0% (95% CI 90.5% to 91.5%) of newly diagnosed T2DM patients requiring treatment were being initiated on this therapy. However, sulfonylureas usage as first-line therapy declined by 2013 to 6.3% (95% CI 5.9% to 6.8%). Few patients with newly diagnosed T2DM were prescribed insulin as first-line therapy in 2013 1.7% (95% CI 1.4% to 1.9%).

Use of thiazolidinediones as first-line therapy remained low and peaked in 2004 (1.1% (95% CI 0.9% to 1.3%)). Other antidiabetic therapies, such as gliptins, GLP-1 analogues, acarbose or meglitinides, were used very rarely as first-line treatments (<1%) in any calendar year.

Table 2 Prevalence of type 2 diabetes mellitus by sociodemographic factors and year

	Prevalence of type 2 diabetes	
	Percentage prevalence (95% CI)	Adjusted IRR (95% CI)*
Overall	4.62 (4.60 to 4.64)	
Gender		
Men	52.90 (52.75 to 53.05)	1
Woman	47.10 (46.95 to 47.25)	0.77 (0.77 to 0.77)
Age, years		
0–9	0.09 (0.08 to 0.09)	0.01 (0.01 to 0.01)
10–19	0.41 (0.39 to 0.43)	0.03 (0.03 to 0.03)
20–29	2.19 (2.15 to 2.23)	0.12 (0.12 to 0.13)
30–39	6.54 (6.47 to 6.61)	0.38 (0.38 to 0.39)
40–49	15.18 (15.07 to 15.28)	1
50–59	27.30 (27.16 to 27.43)	2.28 (2.27 to 2.29)
60–69	37.65 (37.50 to 37.79)	4.13 (4.11 to 4.15)
70–79	36.75 (36.60 to 36.89)	5.95 (5.92 to 5.97)
80–89	22.18 (22.05 to 22.30)	5.59 (5.56 to 5.62)
90–99	4.85 (4.78 to 4.91)	4.00 (3.97 to 4.04)
Townsend quintile		
1	20.23 (20.10 to 20.35)	1
2	19.80 (19.68 to 19.92)	1.12 (1.12 to 1.12)
3	20.74 (20.62 to 20.87)	1.32 (1.32 to 1.33)
4	19.90 (19.78 to 20.02)	1.53 (1.52 to 1.54)
5	14.95 (14.85 to 15.06)	1.75 (1.74 to 1.75)
Year		
2000	2.39 (2.37 to 2.41)	1
2001	2.60 (2.58 to 2.62)	1.10 (1.08 to 1.11)
2002	2.84 (2.83 to 2.86)	1.20 (1.19 to 1.21)
2003	3.11 (3.09 to 3.13)	1.32 (1.30 to 1.33)
2004	3.40 (3.38 to 3.42)	1.44 (1.43 to 1.45)
2005	3.66 (3.64 to 3.67)	1.55 (1.53 to 1.56)
2006	3.88 (3.86 to 3.90)	1.64 (1.63 to 1.65)
2007	4.10 (4.08 to 4.12)	1.73 (1.71 to 1.74)
2008	4.33 (4.32 to 4.35)	1.82 (1.81 to 1.84)
2009	4.56 (4.54 to 4.58)	1.91 (1.90 to 1.93)
2010	4.78 (4.76 to 4.80)	2.01 (1.99 to 2.02)
2011	4.98 (4.96 to 5.00)	2.08 (2.07 to 2.10)
2012	5.17 (5.15 to 5.19)	2.16 (2.14 to 2.18)
2013	5.32 (5.30 to 5.34)	2.21 (2.19 to 2.23)

*Adjusted for other variables considered; gender, age band, Townsend quintile, calendar year, respectively.
†For figure displaying data above, please consult online supplementary appendix 2.

Medicines prescribed as add-on agents after initiation with metformin in patients with newly diagnosed T2DM

Sulfonylureas were the most common add-on therapy used in newly diagnosed patients with T2DM already on metformin between 2000 and 2013; (figure 3 and online supplementary appendix 5). However, sulfonylurea use as an add-on declined from 75.9% (95% CI 72.6% to 79.3%) in 2000 to 61.7% (95% CI 59.2% to 64.2%) in 2013. The use of thiazolidinedione as add-on therapy to metformin peaked in 2002 at 26.9% (95% CI 25.0% to 28.8%), but the prescribing then declined to 1.9% (95% CI 1.2% to 2.7%) by 2013.

Gliptins have become the second most common class of antidiabetic medication added to metformin therapy, with the use at 26.9% (95% CI 24.7% to 29.2%) in 2013. Other antidiabetic therapies were less commonly added on (figure 3).

Medicines prescribed as add-on agents after initiation with sulfonylureas in patients with newly diagnosed T2DM

Metformin was the most common treatment added on to newly diagnosed patients with T2DM on sulfonylureas between 2000 and 2013; (figure 4 and online supplementary appendix 6). In total, 89.8% (95% CI 87.7% to 92.0%) of patients diagnosed with T2DM in 2000 went on to have metformin add-on therapy after a sulfonylurea, while 79.9% (95% CI 74.8% to 85.0%) had metformin added on in 2013.

Insulins were the second most common add-on therapy to sulfonylureas, accounting for 13.4% (95% CI 9.1% to 17.7%) of patients in 2013 (figure 4). Thiazolidinediones and gliptins were the second and third most common add-on therapies, respectively. Prescribing of meglitinides remained <1% throughout, while GLP-1 analogues and acarbose were used in <0.3% of patients as add-on medication in any given year.

DISCUSSION

The incidence of T2DM in UK primary care rose significantly between 2000 and 2005; thereafter, it stabilised around 3.99 per 1000 PYAR in men and 3.73 per 1000 PYAR in women by 2013. Prevalence more than doubled over the duration of the study to 5.3%. Men were 23% more likely to have T2DM and those who were most socially deprived were 75% more likely to have T2DM, as compared to those least deprived. Individuals aged 70–79 years had the highest adjusted prevalence of T2DM, which was nearly six times higher than the reference age band (40–49 years). Prescribing for T2DM also changed considerably over the study, with metformin rising to account for 91.0% of first-line therapy among newly diagnosed patients with T2DM and 79.9% of add-on therapy for patients on sulfonylureas by 2013. Use of gliptin therapy also increased and was used as an add-on medicine in 26.9% of metformin-treated patients; insulin rose to be used as an add-on treatment in 13.4% of patients after a sulfonylurea by 2013.

The incidence of T2DM observed in this study is comparable to data that has been published previously.[20 21] Previous studies were restricted to the period prior to 2010; however, our study includes data up to 2013. The initial rise in diagnoses between 2000 and 2005, and the plateau thereafter may be explained by the lowering of plasma glucose threshold for diagnosis of diabetes in 2000.[5] The increase in incidence observed in 2004 in this study could also relate to the introduction of incentivised payments in the UK as part of the quality and outcomes framework for better monitoring of patients with diabetes mellitus. Women were at greater risk of

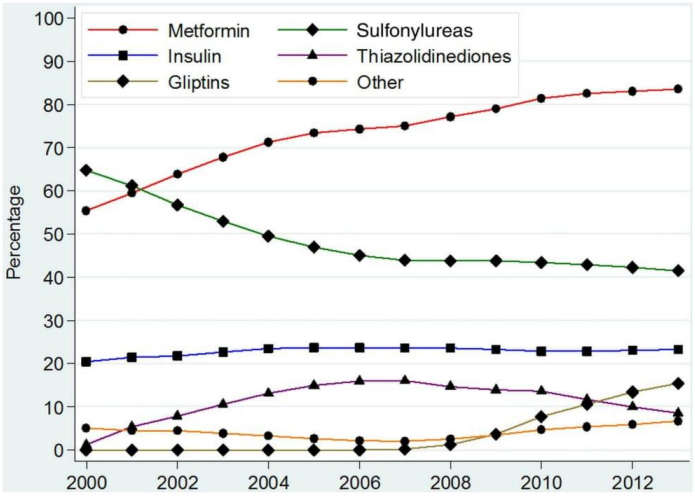

Figure 1 Prevalence of prescribing of different anti-diabetic medications among all patients with type 2 diabetes on treatment.
*Other=Sum of prevalence of Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors.
**For detailed values of point estimates and CIs, please consult online supplementary appendix 3.

developing T2DM relative to men between the ages of 10 and 40 years, in keeping with other published work;[21] after this age, rates increased more significantly in men. Individuals from the most socially deprived areas in our study were at greatest risk of developing the disease. This is of concern as a study in the US has shown a strong association between socioeconomic status and diabetes-related mortality.[22]

The rise in prevalence of T2DM described in this study was similar to that reported by Diabetes UK and the International Diabetes Federation in 2013.[23–25] Prevalence rates of T2DM observed in this study in the UK are similar to what has been observed in other European countries, such as Denmark and Sweden, but lower than that observed in Germany and the US, particularly for the recent years.[26 27]

Similar studies on prescribing conducted with smaller cohorts in the US have shown medication choices to be quite different. For example, in a US cohort study of data between 2009 and 2013 (n=15 516), 57.8% of

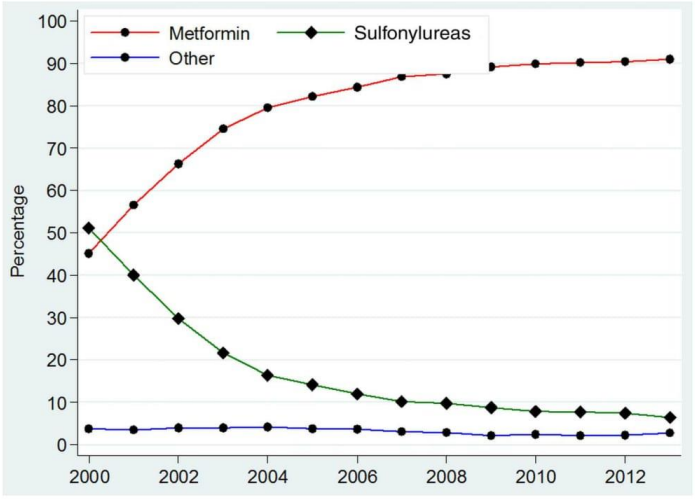

Figure 2 Prevalence of prescribing of different anti-diabetic medications used to initiate treatment in newly diagnosed patients with type 2 diabetes.
*Other=Sum of prevalence of Insulins, Thiazolidinediones, Gliptins, Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors.
**For detailed values of point estimates and CIs, please consult online supplementary appendix 4.

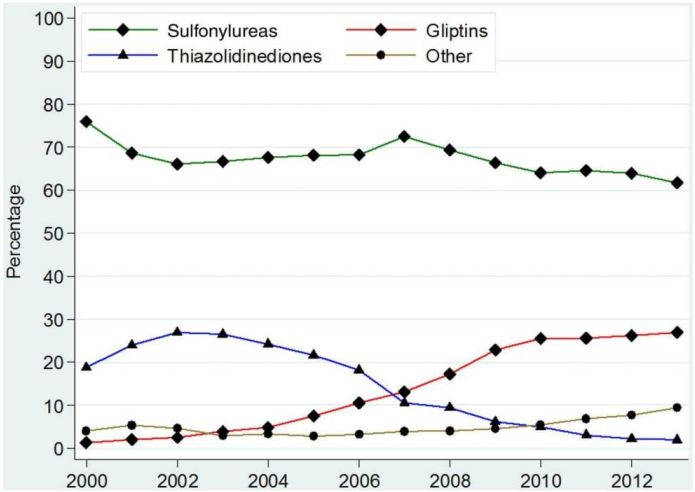

Figure 3 Prevalence of prescribing of different anti-diabetic medications as add-on therapy in patients with type 2 diabetes on metformin.
*Other=Sum of prevalence of Insulins, Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors.
**For detailed figures on point estimates and CIs, please consult online supplementary appendix 5.

patients with T2DM initiated therapy with metformin, 23.0% with sulfonylurea, 13.1% with gliptins and 6.1% with thiazolidinediones,[28] while the corresponding percentages in our study (n=57 518) for the same period 2009–2013 were 90.0%, 7.6%, 0.4% and 0.1%, respectively. This significant selection of metformin over other therapies in the UK suggests an adherence, particularly for treatment initiation, to cost-effective care as published via periodic updates by NICE. This reliance on metformin for first-line therapy has also been evident in other studies conducted in Germany and Denmark, in particular.[29 30]

Metformin use increased steadily from 2000 and was prescribed to 91% of newly diagnosed patients with T2DM requiring treatment in 2013. In 2000, metformin was recommended by NICE for first-line use in obese patients with T2DM only, while non-obese patients were still being recommended sulfonylureas and insulins.[31] However, by 2005, metformin was the recommended first-line treatment choice by all bodies as it is well tolerated,[9 10] does not induce weight gain or hypoglycaemia, and was the only diabetic treatment found to have a long-term benefit in reducing cardiovascular risks and organ damage.[6 10]

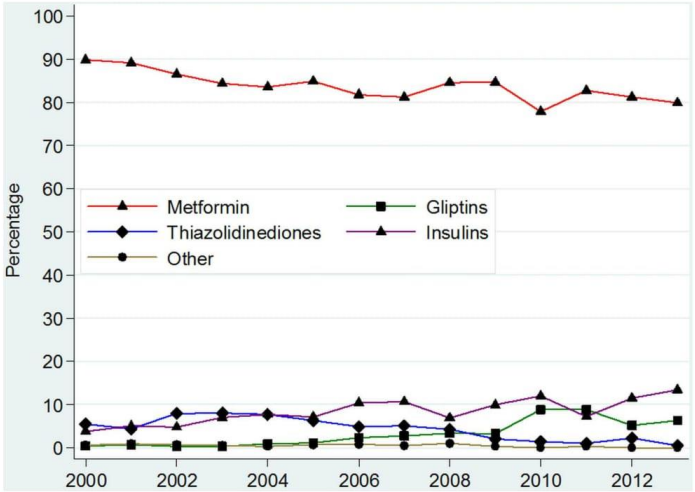

Figure 4 Prevalence of prescribing of different anti-diabetic medications as add-on therapy in patients with type 2 diabetes on sulfonylureas.
*Other=Sum of prevalence of Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors.
**For detailed figures on point estimates and CIs, please consult online supplementary appendix 6.

We found that the use of sulfonylureas as a first-line agent declined among newly diagnosed patients with T2DM, in keeping with published clinical guidance.[9 10] This decline may also be explained by the availability of more treatment options, the risk of weight gain and hypoglycaemia attributed to this class of drugs; and because these were shown not to reduce long-term complications of diabetes.[32 33] Nevertheless, 61.7% of patients with T2DM diagnosed in 2013 still had sulfonylureas added to their metformin treatment.

We observed a decline in thiazolidinedione prescribing after 2003 in response to an increasing awareness of adverse effects of these drugs, such as cardiotoxicity, highlighted in safety alerts for rosiglitazone by regulatory agencies in 2007.[34] Additionally, risks of weight gain, fractures and bladder cancer still exist among currently licensed thiazolidinediones, which may explain their limited use despite evident efficacy.[35]

Since their emergence in 2006, gliptins have rarely been used as first-line therapy in newly diagnosed patients with T2DM. However, their usage as add-on therapy has risen rapidly, perhaps, as they do not induce weight gain or hypoglycaemia.[36] Further increase in gliptin use may depend on data emerging on their long-term benefits for microvascular and macrovascular complications.[37]

GLP-1 analogues were the first antidiabetic treatments to become available that could induce weight loss; however, we have shown that their prescribing in UK primary care particularly as add-on therapy after metformin remains low (1.1%). This is in considerable contrast to prescribing in Denmark where a study examining data for a similar period (2000–2012) provided evidence that nearly 7% of patients with T2DM on metformin had GLP-1 therapy added on.[29] Lower use in the UK may be explained by the publication of the NICE appraisal of the GLP-1 analogue, liraglutide, in 2010 that recommended use of these drugs only in those patients who were already on two other therapies, had high BMIs or were contraindicated to at least three other antidiabetic medications.[38]

A small percentage of newly diagnosed patients with T2DM (1.7%) are still being initiated on insulin and a growing number are having insulin prescribed as add-on therapy. Though current guidance does not support early introduction of insulin, some studies have demonstrated a benefit.[39]

Meglitinides were used in less than 2% of patients annually, between 2000 and 2013. These drugs require multiple daily dosing, carry a risk of inducing hypoglycaemias, and are more costly than sulfonylureas.[9] Use of acarbose has also continued to fall, perhaps as NICE restrict their recommendation to use in patients who cannot tolerate other oral agents.[40] SGLT-2 inhibitors have been the latest class of antidiabetic therapy to emerge; hence, overall prescribing was low (0.5% in 2013). These have been recommended by NICE as add-on treatment, and can aid with weight loss and blood pressure control. They do, however, carry an increased risk of genitourinary tract infections and long-term benefits are unknown.[41 42]

Strengths and limitations of this study

This is the first study, to the best of our knowledge, to detail changes in recording of diagnoses as well as prescribing for T2DM using UK primary care data between 2000 and 2013. We have also provided insight into factors that may have driven these changes. Furthermore, THIN has been shown to be broadly representative of the UK population and a particularly suitable database for drug utilisation work.[11] There are, however, certain limitations to highlight. Though our algorithm for identification of patients with T2DM utilised several variables in addition to diagnostic codes, such as treatment and time of diagnosis, there still remains a risk of some misclassification of T2DM. Also, this study did not measure prescribing of antidiabetic medicines in secondary care. However, it is well established that the majority of prescribing for T2DM is in primary care.[43] We also did not examine prescribing patterns in important clinical subgroups, such as patients with chronic kidney disease, which should be addressed in future work. Prescribing of a medication does not, of course, equate to adherence to therapy. However, the purpose of this study was to examine recording of diagnosis and physician prescribing choices only. Variation in dosages or between drugs within the same therapeutic class were not considered. Some of this has been explored previously.[8]

CONCLUSION

There has been a significant increase in the number of incident and prevalent cases of T2DM between 2000 and 2013. Though the incidence of T2DM has somewhat plateaued since 2005, the prevalence has continued to rise suggesting that patients with T2DM are being diagnosed younger and live longer. Being male, older, and from a more socially deprived area were factors all strongly associated with having T2DM.

Prescribing patterns reflected clinical guidance from NICE, in particular. Metformin emerged as the most widely prescribed agent though sulfonylureas, despite their limitations, remained the second most common therapy prescribed. Latest international guidelines, which may be reflected in future NICE updates, encourage greater use of the broader armamentarium now available for T2DM. We may, therefore, begin to see more varied, patient-specific prescribing. With these and further developments in practice anticipated, it will be important to review in the next few years how prescribing patterns in primary care for T2DM have further changed.

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Contributors MS, IN and IP were all involved in the conception and design of the study. MS performed the analysis, while IN and IP helped with the interpretation. MS prepared the manuscript, and IN and IP helped revise it as needed. All authors have read and approved the final manuscript.

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Competing interests IP, IN and MS report grants from Novo Nordisk A/S during the conduct of this study. They have nothing else to disclose.

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Data sharing statement No additional data are available.

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Correction

Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ Open* 2016;6:e010210.

The data in the original Table 2 showed proportional distribution by gender, social deprivation and age within the dataset rather that population prevalence. We have now replaced this information with estimates of prevalence and the updated Table 2 (see below). Table 2 now includes prevalence estimates by calendar year (as before) as well as prevalence estimates by gender, age and quintiles of Townsend deprivation

Table 2 Prevalence of type 2 diabetes mellitus per 100 individuals by calendar year and by socio-demographic factors for 2013 only

	Prevalence of Type 2 Diabetes in 2013 by socio-demographic factors	
	Percentage Prevalence (95% CI)	Adjusted PR (95% CI)*
Gender		
Men	5.91 (5.88 to 5.94)	1
Woman	5.11 (5.08 to 5.14)	0.79 (0.79 to 0.80)
Age, years		
0–9	0.03 (0.02 to 0.03)	0.01 (0.01 to 0.01)
10–19	0.14 (0.13 to 0.15)	0.03 (0.03 to 0.04)
20–29	0.6 (0.58 to 0.62)	0.15 (0.15 to 0.16)
30–39	1.65 (1.62 to 1.68)	0.42 (0.41 to 0.43)
40–49	3.70 (3.66 to 3.75)	1
50–59	7.76 (7.69 to 7.82)	2.16 (2.13 to 2.20)
60–69	12.95 (12.85 to 13.04)	3.73 (3.67 to 3.79)
70–79	18.75 (18.61 to 18.88)	5.48 (5.40 to 5.56)
80–89	19.29 (19.11 to 19.46)	5.69 (5.60 to 5.78)
90–99	13.44 (13.14 to 13.75)	4.07 (3.96 to 4.19)
Townsend Quintile		
1	5.00 (4.95 to 5.04)	1
2	5.52 (5.47 to 5.56)	1.11 (1.10 to 1.13)
3	5.67 (5.63 to 5.72)	1.31 (1.30 to 1.33)
4	5.94 (5.89 to 5.99)	1.53 (1.51 to 1.54)
5	6.25 (6.19 to 6.31)	1.75 (1.73 to 1.78)
Annual Prevalence of Type 2 Diabetes between 2000–2013		
Year		
2000	2.39 (2.37 to 2.41)	1
2001	2.60 (2.58 to 2.62)	1.10 (1.08 to 1.11)
2002	2.84 (2.83 to 2.86)	1.20 (1.19 to 1.21)
2003	3.11 (3.09 to 3.13)	1.32 (1.30 to 1.33)
2004	3.40 (3.38 to 3.42)	1.44 (1.43 to 1.45)
2005	3.66 (3.64 to 3.67)	1.55 (1.53 to 1.56)
2006	3.88 (3.86 to 3.90)	1.64 (1.63 to 1.65)
2007	4.10 (4.08 to 4.12)	1.73 (1.71 to 1.74)
2008	4.33 (4.32 to 4.35)	1.82 (1.81 to 1.84)
2009	4.56 (4.54 to 4.58)	1.91 (1.90 to 1.93)
2010	4.78 (4.76 to 4.80)	2.01 (1.99 to 2.02)
2011	4.98 (4.96 to 5.00)	2.08 (2.07 to 2.10)
2012	5.17 (5.15 to 5.19)	2.16 (2.14 to 2.18)
2013	5.32 (5.30 to 5.34)	2.21 (2.19 to 2.23)

*PR (prevalence ratios) mutually adjusted for other variables considered; gender, age band, Townsend quintile respectively.
**For figure displaying data above consult online supplementary appendix 2.

for 2013 (the last year of our study period). Related changes have been made to the method, results and discussion section where relevant.

(1) **METHODS/Definition of main outcomes/Prevalence of T2DM** should read:
For our analysis on prevalence of T2DM by calendar year, we included as our numerator all individuals who had a record of T2DM on or before 1st January in the given year and as our denominator we included all patients registered to a general practice on or by 1st January in the given year.

To estimate prevalence by age, gender and social deprivation, we identified numerators and denominators as described above. Given age changed with time we focused on data from 2013 and calculated age at 1st January 2013. Gender and social deprivation were considered as fixed variables.

(2) **METHODS/Statistical Analysis paragraph 2** should read:
The crude prevalence of T2DM for each year was calculated by dividing the number of all individuals recorded as having T2DM on or before 1st January of that year by the total number of patients registered to a general practice on or by 1st January of that year. Multivariable Poisson regression analysis was used to estimate prevalence ratios of T2DM by year adjusted for age, gender and social deprivation as well as mutually adjusted ratios for age, gender and social deprivation for 2013.

(3) **RESULTS/Prevalence of T2DM** from second sentence should read:
Prevalence of T2DM in 2013 was 5.11 per 100 women and 5.91 per 100 men (Prevalence Ratio (PR) 0.79, 95% CI 0.79 to 0.80) (Table 2) and highest among individuals in the most deprived areas (Townsend quintile 5 vs Townsend quintile 1; (PR 1.75, 95% CI 1.73 to 1.78)). The prevalence increased with age. The highest prevalence for T2DM was seen in the 80–89 years age band: 19.29 per 100 individuals (95% CI 19.11 to 19.46). In comparison to individuals aged 40–49, the adjusted prevalence ratio for 80–89 years age band was 5.69, (95% CI 5.60 to 5.78) (Table 2).

(4) **DISCUSSION/Paragraph 1** from third sentence should read:
Data from 2013 showed women were 21% less likely to have T2DM than men and those who were most socially deprived were 75% more likely to have T2DM, as compared to those least deprived. Individuals aged 80–89 years had the highest adjusted prevalence of T2DM, which was nearly six times higher than individuals aged 40–49 years.

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ORIGINAL RESEARCH

An algorithm for identification and classification of individuals with type 1 and type 2 diabetes mellitus in a large primary care database

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Background: Research into diabetes mellitus (DM) often requires a reproducible method for identifying and distinguishing individuals with type 1 DM (T1DM) and type 2 DM (T2DM).

Objectives: To develop a method to identify individuals with T1DM and T2DM using UK primary care electronic health records.

Methods: Using data from The Health Improvement Network primary care database, we developed a two-step algorithm. The first algorithm step identified individuals with potential T1DM or T2DM based on diagnostic records, treatment, and clinical test results. We excluded individuals with records for rarer DM subtypes only. For individuals to be considered diabetic, they needed to have at least two records indicative of DM; one of which was required to be a diagnostic record. We then classified individuals with T1DM and T2DM using the second algorithm step. A combination of diagnostic codes, medication prescribed, age at diagnosis, and whether the case was incident or prevalent were used in this process. We internally validated this classification algorithm through comparison against an independent clinical examination of The Health Improvement Network electronic health records for a random sample of 500 DM individuals.

Results: Out of 9,161,866 individuals aged 0–99 years from 2000 to 2014, we classified 37,693 individuals with T1DM and 418,433 with T2DM, while 1,792 individuals remained unclassified. A small proportion were classified with some uncertainty (1,155 [3.1%] of all individuals with T1DM and 6,139 [1.5%] with T2DM) due to unclear health records. During validation, manual assignment of DM type based on clinical assessment of the entire electronic record and algorithmic assignment led to equivalent classification in all instances.

Conclusion: The majority of individuals with T1DM and T2DM can be readily identified from UK primary care electronic health records. Our approach can be adapted for use in other health care settings.

Keywords: diabetes and endocrinology, epidemiology, public health, databases, algorithm

Introduction

Diabetes mellitus (DM) is a disease characterized by chronic hyperglycemia that occurs due to a deficiency of or resistance to the hormone insulin. It is a major cause of morbidity with estimated 347 million cases worldwide and is expected to become the seventh leading cause of death in the world by 2030.[1] Several subtypes of DM exist, with type 1 DM (T1DM) and type 2 DM (T2DM) being the most widely occurring forms and accounting for over 95% of cases.[2,3] T1DM is an autoimmune disease that peaks in incidence at puberty, though it can manifest at any age and accounts for 5%–10% of all cases of DM.[3] T2DM is an acquired form of DM that is strongly associated with being overweight and accounts for ~90% of all cases of DM.[4] The prevalence

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and incidence of T2DM has been increasing worldwide,[3,5] particularly among older age groups and certain ethnic groups such as people of African, Caribbean, and Southeast Asian origins.[6] Despite an overlap in symptoms, both T1DM and T2DM have different prognoses and are managed differently pharmacologically.[7,8] Individuals with T1DM require insulin for survival due to the lack of insulin production, whereas those with T2DM do not stop producing insulin but develop a resistance to its effects.[3] Management of T2DM is initially through the use of various other antidiabetic agents though they do often progress to needing insulin as well.[7] Other DM subtypes such as gestational diabetes, maturity-onset diabetes of the young, latent autoimmune diabetes in adults, drug-induced diabetes, and even less well-defined idiopathic DM cases account for <5% of all DM cases.[3]

Epidemiological research conducted using electronic health records into DM can provide essential and valuable insight into prevalence, incidence, management, and prognosis of the disease but requires careful and correct identification of DM type to ensure clinical questions are accurately answered. Miscoding, misclassification, and even misdiagnosis are well-established problems with identifying DM type in health records and hence identification and classification of cases can be challenging.[9] This study aims to provide a transparent, reproducible method for classifying diabetics as T1DM and T2DM in UK electronic general practice clinical records that is readily replicable and modifiable for other epidemiological settings.

Materials and methods

Data source

The Health Improvement Network (THIN) primary care database contains anonymized longitudinal electronic health records from 587 primary care practices throughout the UK with over 12 million individuals contributing data. Information available in THIN is collected during routine consultations with general practitioners (family physicians) and health care staff from when an individual registers at a general practice to when they leave the practice or die. THIN is broadly representative of the UK population in terms of patient characteristics, disease burden, and mortality.[10] Data stored in THIN include information on demographics, diagnoses, symptoms of disease, specialist referrals, laboratory testing, disease monitoring, prescribing, secondary care discharge information, and death. Symptoms, diagnosis, and disease monitoring are recorded using Read codes and AHD (Additional Health Data) codes, hierarchical coding systems within medical records, and additional health record files.[11] Using Read code dictionaries, lists can be created to identify individuals with different symptoms and disease.[12] Each unique medication type and strength is given a drug code which can be used for creating drug code lists of medications prescribed.

Study population

All data included in this study were from practices that met quality assurance criteria in THIN, as determined by the acceptable mortality reporting and computer usage standards.[13,14] We included all individuals aged 0–99 years who were registered with a general practice contributing data between 2000 and 2014 and had at least 1 year of quality-assured data following registration.

Algorithm generation

Our method for identifying and then classifying individuals with T1DM and T2DM involved the use of a two-step algorithm. In the first step, we identified all individuals with potential T1DM or T2DM while excluding those coded as having only rarer subtypes of the disease. With the second step, we distinguished cases as having T1DM and T2DM. This two-step algorithm was devised following several discussions within a multidisciplinary clinical research team.

Algorithm step 1 – Identification of individuals with potential T1DM or T2DM

A list of Read codes, drug codes, and AHD codes indicative of DM was prepared. All individuals with any such code indicative of DM in their health record were then identified. We then removed individuals who had no DM records except for metformin prescriptions (probable polycystic ovary syndrome and metabolic disease cases), individuals with only a single record of DM, and individuals who had no diagnostic record (Read code or AHD code) for DM.

Sensitivity analysis on individuals remaining revealed that one particular AHD code being used entitled, "HbA1c diabetic control", was misclassifying cases as DM. Though this code was designed for use in monitoring of DM individuals, exploration revealed that general practitioners were also using this code among nondiabetic and prediabetic individuals as well (potentially for screening purposes). To overcome this problem, individuals who had been assigned as having DM due only to the presence of this code were examined. If they had a HbA1c result above the World Health Organization recommended threshold value of 48 mmol/mol (6.5%), these individuals were classified as having DM; otherwise, they were excluded.[15]

Finally, we excluded individuals with diagnostic codes for other DM subtypes only, for example, gestational diabetes to

obtain the final cohort. The earliest date on which any DM code was recorded was defined as the index date for the start of DM.

Algorithm step 2 – Classification of individuals with T1DM and T2DM

Within the cohort of individuals identified with potential T1DM or T2DM, we generated five variables to help distinguish the DM type. These are listed in a descending level of importance as follows:

- Diagnostic code type assigned
- Cumulative days of noninsulin prescriptions
- Number of insulin prescriptions
- Incident or prevalent case
- Age at first record of DM

Diagnostic code type assigned

We categorized individuals as those who only had T1DM-specific diagnostic codes used in their health record, T2DM-specific codes used in their health record, T1DM- and T2DM-specific codes used in their health record due to diagnostic or coding errors, and finally those with only nonspecific DM diagnostic codes. Examples of Read codes are detailed in Table 1 and in full in the Supplementary material.

Cumulative days of other antidiabetic prescriptions

The number of days an individual was prescribed other antidiabetic (noninsulin) treatment was determined by dividing the quantity of medication issued by the daily dose the individuals were prescribed. In instances where either of these variables was missing, we used a deterministic method of imputing quantity or daily dose based on examination of what was common for that medication quantity or daily dose for individuals whose value were recorded. Where information was completely missing for quantity and daily dose, we assumed prescription was for 28 days as the majority of DM treatments were issued for this duration.

Table 1 Example of diabetes mellitus Read codes

Read code	Description	Code type
C10E611	Type 1 diabetes mellitus with gangrene	T1DM
C108011	Type 1 diabetes mellitus with renal complications	T1DM
C108411	Unstable type 1 diabetes mellitus	T1DM
C10EA00	Type 1 diabetes mellitus without complication	T1DM
C109D11	Type 2 diabetes mellitus with hypoglycemic coma	T2DM
C10F700	Type 2 diabetes mellitus - poor control	T2DM
C10FJ11	Insulin-treated type 2 diabetes mellitus	T2DM
C10F000	Type 2 diabetes mellitus with renal complications	T2DM
C107y00	Other specified diabetes mellitus with peripheral circulatory complications	Nonspecific
2G5I.00	Left diabetic foot at low risk	Nonspecific
ZC2C800	Dietary advice for diabetes mellitus	Nonspecific
F372.11	Diabetic polyneuropathy	Nonspecific

Abbreviations: T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Number of insulin prescriptions issued

The total number of insulin prescriptions issued per individual was also determined. Insulin is needed by individuals with T1DM for survival once the disease has fully set in. However, it is needed less commonly among T2DM individuals, usually for more advanced stages of the disease.[9]

Incident or prevalent case

Mamtani et al showed that if the first record of DM appears for an individual, ≥9 months after registering with a general practice, then that individual is likely to be an incident case of DM.[16]

However, if the first record of DM appears before 9 months in their electronic health record then this is most probably due to the recording of a DM case for someone who already had the disease before practice registration (prevalent).[16] This application was useful as it allowed us to assess whether we potentially had a complete DM record for an individual or whether there was historical DM data for an individual from before practice registration that we may not have access to.

Age of diagnosis of DM

Age of diagnosis of DM was calculated for individuals who were classified as incident cases (first record of DM appearing ≥9 months after practice registration) and for those who had a record of DM that predated their practice registration (entered retrospectively into their health record after practice registration). The first date for a record of DM when preregistration records available were included helped inform when the disease was first diagnosed for that individual. There was a subset of individuals whose first record of DM appeared between 0 and 9 months after practice registration for whom the age of diagnosis could not be confirmed. We used, when necessary, guidance from the Royal College of General Physicians that recommends an age threshold of 35 years for distinguishing individuals with T1DM and T2DM.[9]

Validation

In order to internally validate our classification algorithm, a practically feasible sample of 500 individuals identified with DM was chosen at random from THIN. This sample included both cases classified by the algorithm as T1DM and T2DM.

Each case was then examined and classified into DM type by a clinician independently based on assessment of each individual's full electronic THIN health record consisting of medical, prescription and additional health records. This assessment served as our reference standard. The classification assigned to these 500 individuals by the clinician was then compared with our classification by algorithmic methods to ascertain diagnostic accuracy of the algorithm.

Ethics

THIN has been used for scientific research since approval from the NHS South-East Multi-Centre Research Ethics Committee in 2003. Scientific approval to undertake this study was obtained from CMD Medical Research's Scientific Review Committee in February 2015. (SRC Reference Number: 15-011).

Results

Algorithm step 1 – Identification of individuals with potential T1DM or T2DM

We identified 9,161,866 individuals aged 0–99 years between 2000 and 2014. From this cohort, we identified 457,918 individuals with potential T1DM or T2DM. The number of individuals removed at each step during the application of the algorithm is illustrated in Figure 1.

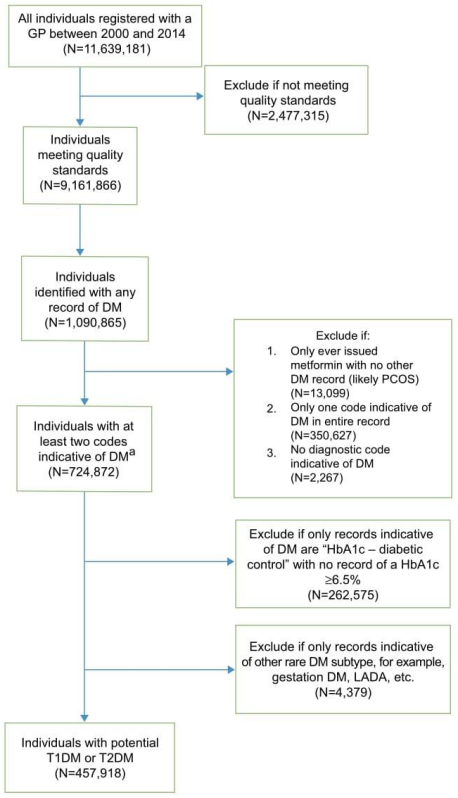

Figure 1 Flowchart for algorithm step 1: Identification of individuals with potential T1DM or T2DM.
Note: [a]Two codes must include at least one diagnostic Read code or AHD code.
Abbreviations: AHD code, Additional Health Data; DM, diabetes mellitus; GP, general practitioner; LADA, latent autoimmune diabetes in adults; PCOS, polycystic ovary syndrome; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; THIN, The Health Improvement Network.

Algorithm step 2 – Classification of individuals with T1DM and T2DM

Of the cohort of 457,918 individuals identified through use of algorithm 1, we classified 37,693 (8.2%) individuals as T1DM; 418,433 (91.4%) as T2DM; and 1,792 (0.4%) remained unclassified (Figure 2). Only 1,155 (3.1%) individuals with T1DM and 6,139 (1.5%) with T2DM were classified with some degree of uncertainty. Thus, the vast majority of individuals were classified with confidence (36,538 [96.9%] individuals with T1DM and 412,294 [98.5%] with T2DM).

The full criteria for classification of individuals into T1DM and T2DM are detailed in Table 2 and summarized below. Unspecific diagnostic codes refer to when both T1DM and T2DM codes were used in the same individual record or when no type-specific code was used to record an individual's DM diagnosis. The individuals classified with uncertainty are highlighted with an asterisk in the following paragraphs and in Table 2.

Individuals with T1DM met one of the following criteria:

1. A diagnostic code of T1DM only and prescription for insulin only.
2. A diagnostic code of T1DM only, a prescription for insulin, and <6 months cumulatively of other antidiabetic agents.
3. A T2DM code only or unspecific diagnostic codes, a prescription for insulin only, and an incident case of DM or diagnosed with DM at <35 years of age.
4. Unspecific diagnostic codes, a prescription for insulin and <6 months cumulatively of other antidiabetic agents, and an incident case of DM or diagnosed with DM at <35 years of age.*

Individuals with T2DM met one of the following criteria:

1. A diagnostic code for T2DM only and any quantity of prescription for other antidiabetic agents with or without insulin.

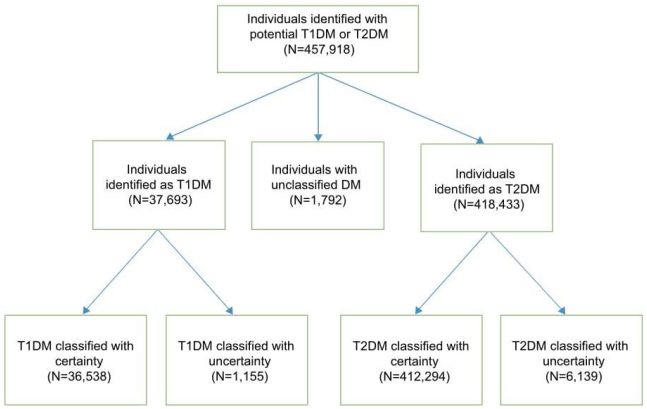

Figure 2 Flowchart for algorithm step 2: Classification of individuals with T1DM and T2DM.
Abbreviations: DM, diabetes mellitus; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

2. A diagnostic code for DM of any type and prescriptions for ≥6 months cumulatively of other antidiabetic agents with or without insulin.
3. A diagnostic code for DM of any type and any quantity of prescription for other antidiabetic agents with no insulin prescription.
4. A diagnostic code for T2DM or unspecific diagnostic codes and no prescribed treatment.
5. A diagnostic code for T1DM only and no prescribed treatment.*
6. A diagnosis of T2DM only or unspecific diagnostic codes, prescribed insulin only, but were a prevalent case and diagnosed with DM at ≥35 years of age.*
7. Unspecific diagnostic codes, prescribed insulin with <6 months cumulatively of other antidiabetic agents, a prevalent case, and diagnosed with DM at ≥35 years of age.*

Uncertainty in classification

T1DM cases classified with uncertainty were those with T2DM or unspecific codes only and up to 6 months of other antidiabetics prescribed in addition to insulin. Though individuals with T1DM do ultimately require insulin for survival, a small proportion of them have a slower onset of disease and may erroneously have other antidiabetics agents prescribed while some residual pancreatic insulin production remains and diagnosis is unclear.[9] Furthermore, it is unusual for T2DM individuals to progress to needing insulin rapidly after diagnosis. For these uncertain cases, we determined if they were incident DM cases and thus whether we had a full history of treatment for that individual. In addition, we also examined the age of diagnosis in cases where there was uncertainty. This is because individuals diagnosed with diabetes at <35 years of age and prescribed insulin were more likely to have T1DM.[9]

T2DM cases classified with uncertainty included individuals with T1DM codes only but not prescribed treatment, individuals with unspecific diagnostic codes and prescribed insulin (and none or <6 months of other antidiabetics), and ≥35 years of age at diagnosis.[9] Though it is rare for T2DM individuals to be managed on insulin alone or progress to needing insulin rapidly after treatment initiation,[7,9] given that they were diagnosed at age ≥35 years and these were prevalent cases that had a history of DM prior to registration that we had incomplete data on, we classified these cases as T2DM but with uncertainty. These uncertain cases represented 1.5% of our total classified T2DM cohort.

Validation

In our internal validation of the classification algorithm using 500 random individuals with DM, the manual assignment of DM type based on clinical assessment of each individual's health record in THIN (reference standard) and algorithmic assignment led to equivalent classification in all instances. Though our sample size was small for feasibility purposes, we observed complete agreement for both T1DM and T2DM classification, hence sensitivity, specificity, positive and negative predictive values were all 100%.

Table 2 Algorithm step 2: classification of individuals with T1DM and T2DM

Type assigned	Code type used	Treatment	Case type	Age at diagnosis	Number
Type 1	T1DM only	Insulin only	–	–	27,942
		Insulin + OAD <6 m	–	–	1,922
	T2DM only	Insulin only	Incident	<35	150
				≥35	1,427
			Prevalent	<35	487
	Unspecific‡	Insulin only	Incident	<35	890
				≥35	1,364
			Prevalent	<35	2,356
		Insulin + OAD <6 m	Incident	<35	238*
				≥35	675*
			Prevalent	<35	242*
Type 2	T1DM only	Insulin + OAD ≥6 m	–	–	3,745
		OAD <6 m	Incident	<35	7
				≥35	13
			Prevalent	<35	8
				≥35	17
		OAD ≥6 m	–	–	107
		No treatment	–	–	611*
	T2DM only	Insulin	Prevalent	≥35	2,975*
		Insulin + OAD <6 m	–	–	2,993
		Insulin + OAD ≥6 m	–	–	45,896
		OAD <6 m	–	–	22,968
		OAD ≥6 m	–	–	202,865
		No treatment	–	–	70,266
	Unspecific‡	Insulin only	Prevalent	≥35	2,043*
		Insulin + OAD <6 m	Prevalent	≥35	510*
		Insulin + OAD ≥6 m	–	–	11,197
		OAD <6 m	–	–	5,775
		OAD ≥6 m	–	–	11,319
		No treatment	–	–	35,118
Unclassified	T1DM only	OAD <6 m	Prevalent	§	17
	T2DM only	Insulin only	Prevalent	§	448
	Unspecific‡	Insulin only	Prevalent	§	1,059
		Insulin + OAD <6 m	Prevalent	§	268

Notes: ‡T1DM and T2DM codes or nonspecific codes; *individuals classified with a degree of uncertainty; §age of diagnosis could not be confirmed.
Abbreviations: OAD, other antidiabetics; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Discussion

In this study, we described a two-step algorithm to identify and classify individuals with T1DM and T2DM in a large UK primary care database and demonstrated that the vast majority of individuals can be classified with confidence: 36,538 (96.9%) individuals with T1DM and 412,294 (98.5%) with T2DM.

Other algorithms have been previously developed in clinical studies to identify individuals with T2DM specifically,[17] and advise on how to diagnostically distinguish T1DM from T2DM.[9] There was, however, an absence of a clear approach for distinguishing between T1DM and T2DM in a general practice database such as THIN.

The main strengths of this two-step algorithm are that it identifies and classifies the majority of individuals with T1DM and T2DM with confidence and clearly outlines individuals for whom classification is challenging and where it is not possible. This means that depending on the clinical question of interest, the DM cohort chosen for the study can be modified; for example, by excluding individuals classified with uncertainty, one can ensure greater confidence in classification in the cohort. Additionally, code lists were generated by two researchers independently and reviewed by a clinician, and our internal validation showed high diagnostic accuracy for the algorithm. The values of this algorithm has also been demonstrated in published studies where incidence, prevalence, and prescribing patterns for T2DM were shown to compare favorably with data collected by other UK and international bodies.[5,18]

Though this algorithm is mostly suited for use in the UK general practice databases such as THIN and Clinical Practice Research Datalink, they can be adapted for use in

epidemiological research for other settings. International Classification of Diseases 10 codes or other hierarchical coding systems indicative of DM could be used instead of Read codes, whereas pharmacological therapy and thresholds for the age at diagnosis could be modified as necessary according to local treatment and monitoring guidelines.

The quality and outcomes framework introduced as part of the GP contract for the UK in 2004 brought in several indicators for DM to help improve disease management.[19] However, as financial incentives were introduced for the use of certain T1DM- and T2DM-specific codes, overzealous recording may have led to erroneous diagnoses.[9] Our algorithm considers medications prescribed, HbA1c results, age of diagnosis, and whether a case is incident or prevalent, which will reduce such errors.

There are, however, some limitations to acknowledge. In this study, we did not seek validation by comparison of our classification systems based on the algorithm to complete patient case notes. This would further strengthen the case for use of this algorithm. The sample of 500 records for internal validation was chosen for feasibility purposes however given the significant size of the cohort, a larger sample size may have been preferable to ensure more accurate validation. Markers such as body mass index and ethnicity can potentially be used to additionally support DM type classification. Body mass index is generally higher among individuals with T2DM rather than T1DM,[20] whereas T2DM is known to be more prevalent among certain ethnic groups.[21] However, given the variables we included already facilitated confident classification for 98.0% of our cohort, we did not investigate further.

We excluded cases with only diagnostic codes related to rarer subtypes of DM such as maturity-onset diabetes of the young, latent autoimmune diabetes in adults, drug-induced diabetes, and gestational diabetes. This, of course, cannot guarantee that some miscoded and misdiagnosed cases did not enter our cohort. In other epidemiological settings, where complete data for secondary care are also available, women with gestational diabetes having their first and final record of DM while pregnant could also be excluded.

Electronic health records in THIN are dynamic, that is, individuals register and leave the general practices at different points in time and some individuals have been registered for much longer than others. Individuals with only a short duration of registration may not have a DM diagnosis entered in their records or a sufficient time to be issued treatment for DM. Therefore, varying record lengths can risk introducing bias. When this algorithm is applied to other datasets, it is worth noting that the longer the record lengths following the first record of DM, the lower the risk of any such bias will be. Finally, with recent recommendations by bodies such as the National Institute for Health and Care Excellence in 2015 to consider prescribing metformin for T1DM individuals with higher body mass index, this treatment combination is likely to become increasingly common. Thus, the algorithm will need to be adapted for use in future years. This could be achieved by further scrutinizing the records of individuals on metformin and insulins only, for indicators that may help distinguish them as T1DM or T2DM such as diagnostic codes and age of diagnosis.[8]

Conclusion

We have provided a transparent and reproducible method with which the vast majority of individuals with T1DM and T2DM can be identified with confidence in primary care databases such as THIN and the Clinical Practice Research Database. With some modifications accounting for dataset type and hierarchical coding systems employed, the two-step algorithm we provide can also be applied to other electronic health record databases both in the UK and worldwide. The algorithm is flexible and can be modified as needed to vary the level of confidence in classification needed to help identify individuals with DM of interest for different epidemiological studies.

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Author contributions

MS, IP, IN, and SJC collectively planned the study and writing of the manuscript. MS performed the analysis and with IP, IN and SJC interpreted the results. MS drafted the manuscript, IP, IN, and SJC revised it critically for content. MS, IP, IN, and SJC agreed the final version to be published.

Disclosure

The authors report no conflicts of interest in this work.

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BMJ Open

Effectiveness of sitagliptin compared to sulfonylureas for type 2 diabetes mellitus inadequately controlled on metformin: a systematic review and meta-analysis

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ABSTRACT

Objective To assess the effectiveness of sitagliptin compared to sulfonylureas as add-on to metformin in adults with type 2 diabetes mellitus from both randomised controlled trials (RCTs) and 'real-world' non-randomised studies.

Methods and analyses We conducted a systematic review of EMBASE, MEDLINE, CENTRAL and grey literature for RCTs and non-randomised studies. We reported outcomes relating to change in HbA1c, fasting glucose, weight, blood pressure and lipids from baseline and need for treatment change. No study investigating macrovascular and microvascular diabetes complications was found. Meta-analysis was used where studies were sufficiently homogenous.

Results Seven RCTs and five non-randomised studies were eligible for inclusion from 1335 articles retrieved. Meta-analysis of three homogenous RCTs revealed a statistically significant decrease in weight with sitagliptin when compared to sulfonylureas (weighted mean difference (WMD) −2.05 kg; 95% CI −2.38 to −1.71); however, a similar change from baseline in HbA1c (WMD 0.05; 95% CI −0.03 to 0.12), fasting glucose (WMD 0.11; 95% CI −0.08 to −0.29), blood pressure, lipids and the proportion achieving HbA1c <7% by study end (OR 0.98; 95% CI 0.85 to 1.13) was observed. Non-randomised studies identified consisted of four prospective and one retrospective cohort study. Three of these five studies were of moderate/high quality, and results though less precise suggested similar real-world comparative glycaemic and weight effectiveness for both treatments. Data from two cohort studies suggested that treatment change (HR 0.65; 95% CI 0.57 to 0.73) and insulin initiation (HR 0.76; 95% CI 0.65 to 0.90) were less likely among those prescribed sitagliptin; however, inadequate reporting of HbA1c at time of treatment change made interpreting results challenging.

Conclusion Sitagliptin users experienced modest weight loss compared to gain with sulfonylureas; however, this difference was around 2 kg, which may not be of major clinical significance for most individuals. Similar change was observed across most other effectiveness outcomes reported. Further studies are needed to address longer-term effectiveness outcomes for sitagliptin compared to sulfonylureas as add-on to metformin.

PROSPERO registration number CRD42016033983.

Strengths and limitations of this study

- ► We provide a comprehensive overview examining a wide range of effectiveness outcomes for sitagliptin versus sulfonylureas as add-on to metformin.
- ► We assess and report evidence from both randomised clinical trials and 'real-world' non-randomised studies.
- ► We have undertaken and presented meta-analysis where methodologically appropriate.
- ► We have focused on effectiveness issues only in this review as safety has been evaluated in depth elsewhere; however, we have summarised the safety literature in our introduction.
- ► We have focused on sitagliptin only as this is the most widely prescribed dipeptidyl-peptidase-4 inhibitor in the UK.

INTRODUCTION

Management of patients with type 2 diabetes mellitus (T2DM) is complex and often requires multiple pharmacological treatments to achieve adequate control of the disease.[1 2] Most clinical guidelines recommend metformin as initial monotherapy; however, there is no consensus on second-line treatment.[1–4] This is further complicated by the increasing number of pharmacological treatments options now available. Dipeptidyl-peptidase-4 (DPP-4) inhibitors and sulfonylureas represent two of the largest classes of therapy prescribed worldwide.[5 6] Sitagliptin has been the most extensively prescribed DPP-4 inhibitor in the UK and USA,[7] while alongside metformin, sulfonylureas such as gliclazide are the most widely prescribed oral antidiabetic agent for T2DM.[5] Sitagliptin slows the inactivation of incretin hormones (glucagon-like-peptide-1 and glucose insulinotropic peptides), which in turn increase insulin synthesis and release and suppress

glucagon release.[8] Sulfonylureas, however, work solely through increasing insulin secretion via direct stimulation of β-cells in the pancreas.[8] Clinicians often have to choose between prescribing sitagliptin or a sulfonylurea as potential options to add-on in patients with T2DM inadequately controlled on metformin.[5]

Clinical guidance from the American Association of Clinical Endocrinologists now recommends sitagliptin usage over sulfonylureas for second-line treatment[9]; however, most other major international guidelines such as those from the UK National Institute of Heath and Care Excellence, American Diabetes Association, European Association for study of Diabetes and International Diabetes Federation do not significantly discriminate between treatments and advocate that either may be selected as potential options to add-on, having accounted for patient preferences and medication safety.[1–4] Medication safety takes priority across Asian clinical guidelines as well, which tend to be individualised across most countries[10]; however, studies have shown increasing usage of both treatments particularly in Eastern Asian countries as well.[6]

From a safety perspective, both sulfonylureas and sitagliptin have been studied in considerable depth. To summarise, a several-fold higher risk of hypoglycaemia has been well established with sulfonylureas across adult and several vulnerable population groups such as older individuals.[11–14] An increased risk of pancreatitis with sitagliptin has also been reported,[15] though absolute risk appears low, while conflicting evidence regarding a worsening of heart failure in patients prescribed sitagliptin has been signalled.[8 16]

Though safety of both treatments has been well evaluated, less has been characterised about the comparative effectiveness of sitagliptin compared to sulfonylureas from both randomised controlled trials (RCTs) and non-randomised studies using 'real-world' data.

Several randomised placebo controlled trials have been conducted on both sitagliptin and sulfonylureas[17–20]; however, these do not facilitate direct comparison between the two. We carried out a systematic review to collate and analyse evidence from both RCTs and non-randomised studies to ascertain the effectiveness of sitagliptin compared to sulfonylureas in patients inadequately controlled on metformin. We examined a wide range of clinical effectiveness outcomes for which data have been reported.

METHODS

We conducted this systematic review in accordance with a prespecified published protocol.[21] We have reported our findings in order to comply with both the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) statement and MOOSE (Meta-Analyses and Systematic Reviews of Observational Studies) reporting guidelines.[22 23]

Eligibility criteria

A study was eligible if it was an RCT or non-randomised study conducted postmarketing authorisation comparing sitagliptin with sulfonylureas (gliclazide, glipizide, glibenclamide, tolbutamide, chlorpropamide, glimepiride) in adults with T2DM inadequately controlled on metformin. We required that all studies have a minimum of 1-month patient follow-up after initiation with sitagliptin or sulfonylurea for outcomes (however, a minimum of 3 months was required for reported changes in HbA1c).

Search strategy and study selection

Eligible studies written in English were identified using electronic searches for RCTs, non-randomised observational studies and conference abstracts using MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to 1 June 2016 and EMBASE (1 January 1980 to 1 June 2016). Search strategies were developed for individual databases and reviewed by an information specialist to ensure rigour (online supplementary methods 1a–2c). Additional studies and grey literature were retrieved by screening references of retrieved studies and by searching International Pharmacy Abstracts, conference proceedings on Scopus and the WHO international clinical trial registry. We also contacted authors and manufacturers directly in cases where data were not available in the public domain; however, no additional data were made available.

One reviewer (MS) performed the full search strategy, removed duplicates and selected the articles. A second reviewer (NB) independently analysed these selections for eligibility of inclusion. Studies were screened based on title and abstract initially, following which full texts were obtained and assessed for inclusion. All records identified in searches were managed and stored in a reference management software (EndNote X7, Thomson Reuters, New York, USA).

Data extraction

All data were independently extracted by two reviewers (MS and NB) into standardised electronic forms. Data extracted included study details, participant details and intervention details (drug name, dose, frequency). Reported intention-to-treat analysis results were used where possible. Outcomes examined compared sitagliptin and sulfonylurea for change from baseline in HbA1c (%), fasting plasma glucose (mmol/l), weight (kg), body mass index (BMI) (kg/m^2), systolic and diastolic blood pressure (mm Hg), total cholesterol (mmol/mol) and triglycerides (mmol/mol) and the number of individuals achieving HbA1C at study end of <7% and <6.5%. In addition, all data on longer-term outcomes involving over 2 years of patient follow-up where reported were also extracted. This included data examining the risk of needing treatment change or insulin initiation after commencement of sitagliptin compared to sulfonylureas. We also proposed to extract data on longer-term outcomes examining risk of macrovascular and microvascular

complications of diabetes; however, no such data were retrieved. All disagreements between reviewers were resolved by consensus or discussion with a third (IN) and fourth reviewer (IP) where needed.

Quality assessment

The Cochrane Collaborations Risk of Bias Tool was used to assess heterogeneity and quality for the RCTs. All six domains in the risk of bias tool were assessed: random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each domain was graded as (a) low bias, (b) unclear bias or (c) high bias.[24]

The methodological quality of non-randomised studies included was assessed using the Newcastle-Ottawa Quality Assessment Scale.[25] This scale consists of a 'star-rating system' in which a study is judged on three broad domains: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.[25]

All study assessments were carried out independently by two reviewers and checked for agreement. Differences were resolved through consensus or in consultation with a third (IN) and fourth reviewer (IP).

Data analysis

Mean differences (MDs) were calculated for continuous outcomes and ORs or HRs for dichotomous outcomes where possible. Adjusted data (adjusted OR or HR with 95% CI) from non-randomised studies were used where available. We planned to conduct meta-analysis if included articles were sufficiently homogenous and of high quality. However, given the wide range of research methods identified, significant variation in duration of follow-up across studies and overlapping patient populations in some studies, a meta-analysis across all studies was not deemed appropriate. Nonetheless, forest plots were constructed for comparison and an overall descriptive analysis was undertaken examining each outcome across the studies where reported with a comprehensive account of study quality.

We did undertake meta-analysis for outcomes where two or more studies were available of a sufficiently homogenous standard. Data synthesis was undertaken using a fixed-effects model (Mantel-Haenszel method) unless our assessment of study qualities determined that a fixed-effects model was unsuitable or significant heterogeneity was evident.[26] Heterogeneity was assessed using the I^2 statistic, with an I^2 statistic greater than 50% considered indicative of significant heterogeneity and necessitating use of a random-effects model (Dersimonian-Laird method) for meta-analysis.[24 27]

Sensitivity analysis undertaken to explore impact of duration of follow-up on meta-analysis results did not alter findings. All analysis was undertaken using STATA statistical software package (version 13).

RESULTS

Search results and study characteristics

In total, 12 studies were eligible for inclusion (figure 1) with a list of excluded studies following full text review in the online supplementary table S1. Included studies consisted of seven RCTs[28–34] and five non-randomised (table 1).[35–39] Among the RCTs, four studies used glimepiride exclusively as the sulfonylurea comparator,[28–30 34] two studies exclusively used glipizide,[32 33] while one study used glibenclamide.[31] Among the non-randomised studies, use of various sulfonylureas were permitted. Duration of patient follow-up in the RCT studies ranged from 1 month for the shortest[30] to 24 months for the longest studies.[28 33] Duration of patient follow-up was, in general, longer in the non-randomised studies ranging from 3 months in the shortest prospective cohort study[38] to 72 months in the longest.[36] Four of the seven RCT studies required patients to be on metformin at a dose of ≥1500 mg at baseline,[28 29 32 33] while this was not required for any of the non-randomised studies. Further details on study exclusion criteria can be found in online supplementary table S2.

The characteristics of participants across the studies are summarised in table 2. The study population ranged from 34 individuals in the smallest RCT[30] to 1172 in the largest.[33] Non-randomised study sizes ranged from 69 participants to 20 529 individuals in the largest cohort study.[36 37] The mean age of participants ranged from 54.3 years to 59.6 years in the RCTs and 46.9 years to 64.2 years in the non-randomised studies. The mean baseline HbA1c ranged from 7.0% to 8.3% in the RCT, while it ranged from 7.5% to 8.7% across the non-randomised studies. Mean weight at baseline ranged from 80.6 kg to 91.8 kg in the RCTs, while it ranged from 63.8 kg to 74.5 kg in the non-randomised studies; however, it was often poorly reported.

Quality assessment

Risk of bias assessment for RCTs

Out of seven RCTs, three studies were judged to be at high risk of bias in one of the seven domains examined as shown in online supplementary table S3. A lack of blinding of participants and personnel put both Srivastava *et al* and Koren *et al* at high risk of bias.[31 34] Additionally, Koren *et al* was also deemed to be at high risk of selection bias due to the absence of adequate randomisation of participants.[31] Kim *et al* was at high risk of reporting bias as all outcomes, for example, change in HbA1c were reported in absolute terms without adjustment (despite imbalance in gender and baseline fasting plasma glucose after randomisation) and no comparative analysis examining both treatments was undertaken.[30] In Kim *et al*, it was unclear whether sequence generation for randomisation was inadequate or baseline imbalances were simply due to the small sample size for the study of 34. However, this lack of adjustment in analysis meant any results presented in Kim *et al* could not be used for our comparative analysis. Risk of other bias was also high for

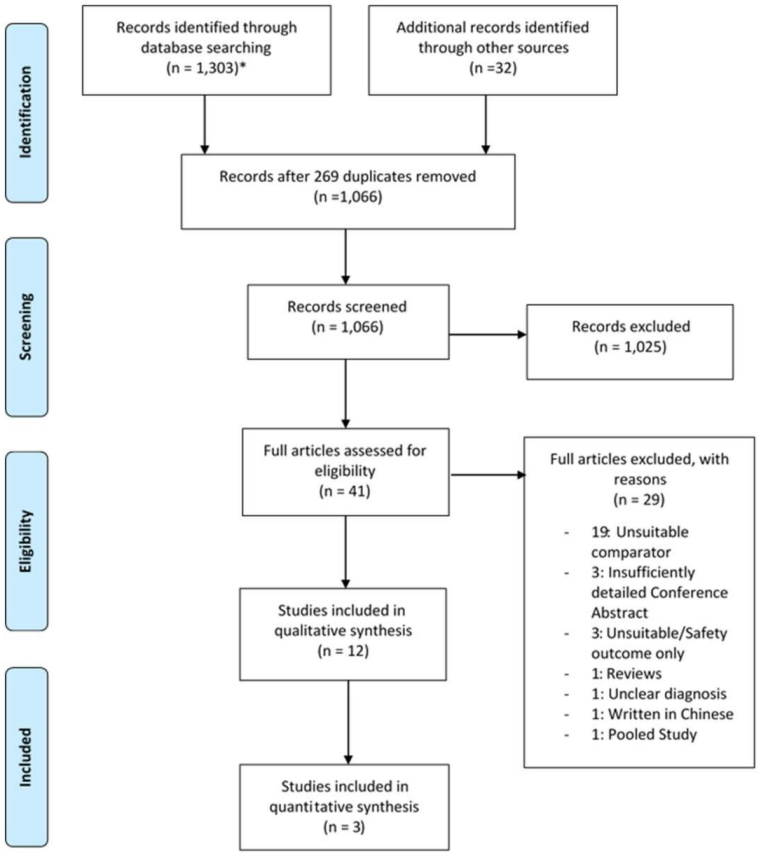

Figure 1 PRISMA flow diagram: study identification, selection and exclusions. *Monthly automated alerts from 01/11/15 to 01/06/16 consisting of updates to the search strategy identified additional articles in Embase, Medline and CENTRAL that have been included in the flow diagram above. However, no eligible studies for inclusion were obtained through these updates

Srivastava *et al* due to a lack of information on baseline characteristics of study participants, which made the final study results challenging to interpret.[34]

Assessment of study quality of non-randomised observational studies using Newcastle-Ottawa Scale

Based on use of the Newcastle-Ottawa Scale described earlier, two of the five non-randomised studies were deemed to be of low quality as shown in online supplementary table S4. Suraj *et al* achieved a low-quality rating as it did not meet the standard expected for cohort comparability mainly due to a failure to adjust for important confounders such as age, sex, baseline HbA1c, weight and metformin dose in the final analysis.[38] Derosa *et al* achieved a low-quality rating as they had a strict cohort study exclusion criteria excluding more ill diabetic patients, and though they matched for age, sex and diabetes duration, they failed to adjust for other potential relevant confounders such as socioeconomic status, comorbidities, among others. Derosa *et al* also had significant loss to follow-up and failed to describe it with sufficient clarity or evaluate whether this may have biased results.[35] Further details on methodological approaches used to control confounding in each of the five non-randomised studies are provided in online supplementary table S5.

Outcomes

Glycaemic change

Seven studies in total reported glycaemic change (figure 2A). We performed meta-analysis for three of these RCTs because they were of high quality and exceeded 6 months in duration. A fourth study, led by Nauck *et al*, could not be included for meta-analysis, as

Table 1 Characteristics of the included studies

Study	Type	Sita dose	Sulf dose	Duration*	Inclusion criteria	Primary outcome
Ahrén *et al*†[28]	RCT	100 mg	Glim 2–4 mg	24	Aged ≥18 years and T2DM and baseline HbA1c ≥7.0% and ≤10.0% and prescribed metformin ≥1500 mg or maximum tolerated dose, BMI 20–45 kg/m^2; creatinine clearance >60 mL/min; normal thyroid-stimulating hormone concentration or clinically euthyroid	Change in HbA1C from baseline
Arechavaleta *et al*[29]	RCT	100 mg	Glim 1–6 mg	7.5	Aged ≥18 years with T2DM and baseline HbA1c ≥6.5% and ≤9.0% and prescribed metformin ≥1500 mg/day	Change in HbA1C from baseline
Kim *et al*[30]	RCT	100 mg	Glim 2 mg	1	Aged 18–80 years and T2DM for <10 years baseline HbA1c ≥7.0% and ≤10.0% prescribed metformin and BMI 20–30 kg/m^2	Change in HbA1C from baseline
Koren *et al*[31]	RCT	100 mg	Glib 5 mg	3	Aged 18–75 years and T2DM with baseline HbA1c ≥7.0% and prescribed metformin	Change in arterial stiffness from baseline
Nauck *et al*[32]	RCT	100 mg	Glip 5–20 mg	12	Aged 18–78 years and T2DM and baseline HbA1c ≥6.5% and ≤10.0% and prescribed metformin ≥1500 mg/day	Change in HbA1C from baseline
Seck *et al*‡[33]	RCT	100 mg	Glip 5–20 mg	24	Aged 18–78 years and T2DM and baseline HbA1c ≥6.5% and ≤10.0% and prescribed metformin ≥1500 mg/day	Change in HbA1C from baseline
Srivastava *et al*[34]	RCT	50–200 mg	Glim 1–4 mg	4.5	Aged ≥18 years with T2DM and baseline HbA1c ≥7.0% and ≤10.0% and prescribed metformin	Change in HbA1C from baseline
Derosa *et al*[35]	Prosp. Cohort	100 mg	Var§	60	Aged >18 years with T2DM and baseline HbA1c ≥8.0%, prescribed metformin and BMI 25–30 kg/m^2).	Change in HbA1C from baseline
Inzucchi *et al*[36]	Retro. Cohort	Var	Var§	72	Aged ≥18 years, initiated therapy with metformin in the 12 months preceding the index date on which sitagliptin/sulfonylurea initiated	Risk of insulin initiation
Lee *et al*[37]	Prosp. Cohort	100 mg	Var§	6	Aged ≥18 years with T2DM with a baseline HbA1c level ≥7.5% and prescribed metformin	Change in HbA1C from baseline
Suraj *et al*[38]	Prosp. Cohort	100 mg	Var§	3	Aged 18–70 years with T2DM and a baseline HbA1c ≥7.0% and prescribed metformin	Change in HbA1C from baseline
Valensi *et al*[39]	Prosp. Cohort	100 mg	Var§	36	Aged ≥18 years and prescribed metformin with inadequately controlled T2DM as determined by physician judgement	Risk of need for treatment change

*Duration reported in months.
†Only sitagliptin and sulfonylurea RCT arms considered.
‡Seck *et al* is an extended follow-up study of Nauck *et al*; only Seck *et al* was included for meta-analysis.
§Use of any sulfonylurea drug was permitted. In Suraj *et al*, 5 mg glibenclamide, 1 mg glimepiride or 60 mg gliclazide were permitted only.
BMI, body mass index; Glib, glibenclamide; Glim, glimepiride; Glip, glipizide; HbA1c, haemoglobin A1c; Prosp, prospective; RCT, randomised controlled trial; Retro, retrospective; Sita, sitagliptin; Sulf, sulfonylureas; T2DM, type 2 diabetes mellitus.

Table 2 Patient characteristics across the included studies

Study	Participants		Age (SD)		Male (n) (%)		Diabetes duration (years) (SD)		HbA1c (%) (SD) (mmol/mol, SD)		FPG (mmol/l) (SD)		Weight (kg) (SD)	
	Sita	Suf	Sita	Suf	Sita	Suf	Sita	Suf	Sita	Suf	Sita	Suf	Sita	Suf
Ahrén *et al*[28]	302	307	54.3 (9.8)	54.4 (10.0)	139 (46.0)	158 (51.5)	5.8 (4.8)	6.0 (4.8)	8.1 (0.8) (65, 8.7)	8.1 (0.8) (65, 8.7)	9.2 (2.6)	9.3 (2.5)	90.3 (19.1)	91.8 (20.4)
Arechavaleta *et al*[29]	516	519	56.3 (9.7)	56.2 (10.1)	284 (55.0)	279 (53.8)	6.8 (4.6)	6.7 (4.8)	7.5 (0.7) (58, 7.7)	7.5 (0.8) (58, 8.7)	8.0 (1.8)	8.1 (19)	80.6 (15.2)	82.0 (16.7)
Kim *et al*[30]	17	17	59.6 (6.7)	55.8 (6.6)	12 (75.0)	7 (41.2)	4.8 (5.2)	5.9 (4.2)	7.0 (0.5) (53, 5.5)	7.3 (0.4) (56, 4.4)	7.3 (0.5)	8.7 (0.7)	NR	NR
Koren *et al[31]**	40	40	59.0 (10.0)	59.0 (10.0)	25 (62.5)	25 (62.5)	7.8 (5.0)	7.8 (5.0)	8.3 (1.1) (67, 12)	8.3 (1.1) (67, 12)	9.4 (0.7)	9.4 (0.7)	NR	NR
Nauck *et al*[32]	588	584	56.8 (9.3)	56.6 (9.8)	336 (57.1)	358 (61.3)	6.5 (6.1)	6.2 (5.4)	7.7 (0.9) (61, 9.8)	7.6 (0.9) (60, 9.8)	9.2 (2.3)	9.1 (2.3)	89.5 (17.4)	89.7 (17.5)
Seck *et al*§[33]	588	584	56.8 (9.3)	56.6 (9.8)	336 (57.1)	358 (61.3)	6.5 (6.1)	6.2 (5.4)	7.7 (0.9) (61, 9.8)	7.6 (0.9) (60, 9.8)	9.2 (2.3)	9.1 (2.3)	89.5 (17.4)	89.7 (17.5)
Srivastava *et al*[34]	25	25	NR	NR	NR	NR	NR	NR	8.3 (0.4) (67, 4.4)	8.2 (0.6) (66, 6.6)	10.2 (0.6)	9.9 (0.7)	NR	NR
Derosa *et al*[35]	216	NR†	NR	NR	NR	NR	NR	NR	8.3 (0.3) (67, 3.3)	8.5 (0.5) (69, 5.5)	8.1 (0.8)	8.3 (0.9)	NR	NR
Inzucchi *et al*[36]	6104	14425	57.4 (11.8)	58.0 (12.5)	3074 (50.4)	7504 (52.0)	NR	NR	7.9 (1.6) (63, 17.5)	8.4 (2.0) (68, 21.9)	NR	NR	NR	NR
Lee *et al*[37]	38	31	50.2 (13.7)	54.8 (11.6)	24 (63.2)	16 (51.6)	1 (0.6)‡	1 (0, 12)‡	9.4 (7.9, 11.1) ‡ (79 (63, 98))	8.9 (8.2, 10.2) ‡ (74 (66, 88))	9.6 (7.5, 11.3)‡	9.3 (7.7, 10.8)‡	74.5 (11.6)	69.9 (15.4)
Suraj *et al*[38]	50	50	46.9 (9.6)	48.9 (9.3)	34 (68.0)	19 (38.0)	3.4 (3.5)	2.8 (3.0)	8.2 (1.0) (66, 10.9)	8.7 (1.4) (72, 15.3)	10.2 (3.2)	10.8 (3.4)	65 (12.2)	63.8 (9.7)
Valensi *et al*[39]	1874	733	62.4 (10.8)	64.2 (11.5)	1108 (59.4)	422 (57.6)	6.4 (5.9)	7.0 (5.6)	7.5 (1.0) (58, 10.9)	7.6 (1.0) (60, 10.9)	8.6 (2.1)	8.5 (2.2)	NR	NR

*Crossover trial; hence, characteristics are the same in both arms.
†In Derosa *et al*, the authors compared several groups of patients prescribed with metformin (metformin and sulfonylurea, metformin and pioglitazone) and did not detail how many were in the metformin and sulfonylurea group specifically.
‡Median and IQR reported (not mean).
§Seck *et al* is an extended follow-up study of Nauck *et al*; only Seck *et al* was included for meta-analysis.
hbA1c, haemoglobin A1c, FPG, fasting plasma glucose; NR, not reported; SD, standard deviation; Sita, sitagliptin; Sulf, sulfonylureas.

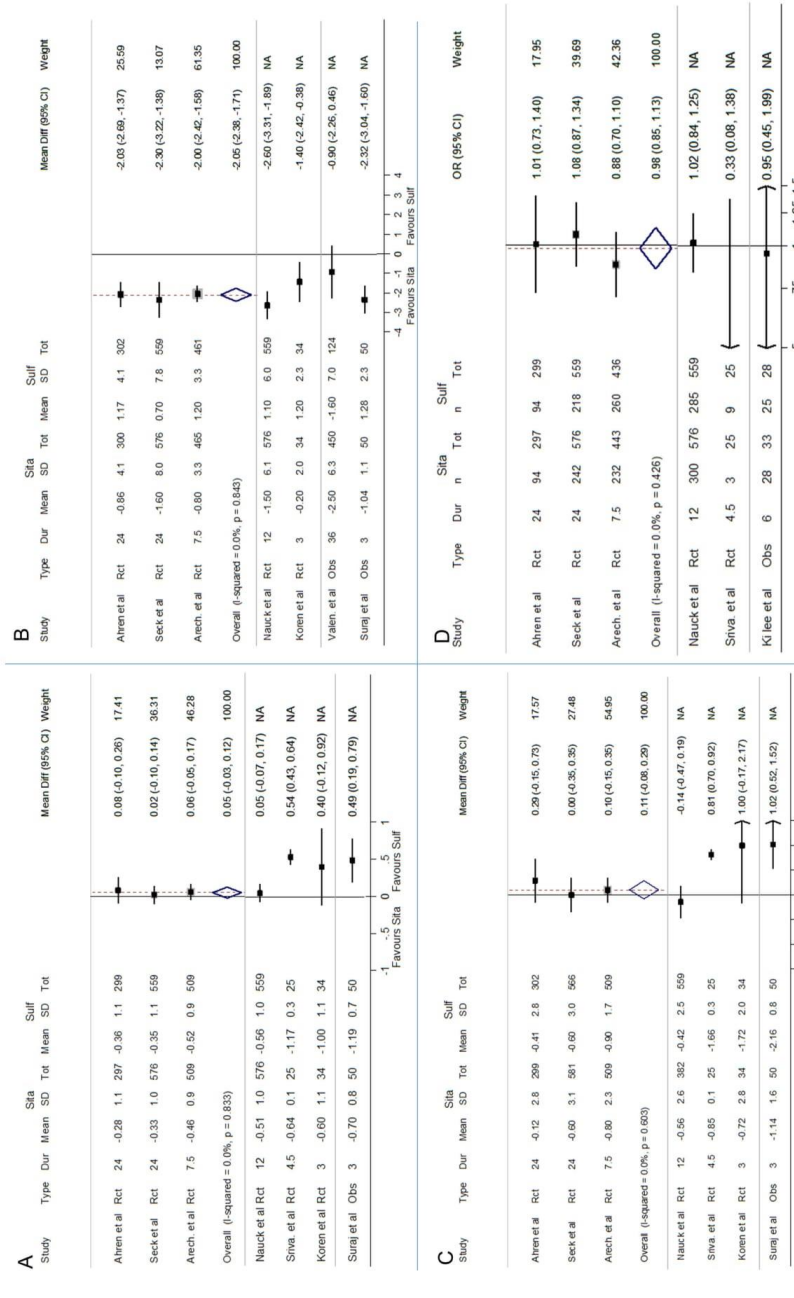

Figure 2 Forest plots comparing sitagliptin and sulfonylureas for change from baseline in hbA1c (%) (A), weight (kg) (B), fasting plasma glucose (mmol/mol) (C) and for proportions achieving a hbA1c <7% (53 mmol/mol) at end of study (D). Dur, duration in months; Mean Diff, mean difference; NA, not applicable; Obs, Non-randomized Observational study; OR, Odds ratio; Rct, Randomized controlled trial; SD, Standard deviation; Sita, sitagliptin; Sulf, sulfonylureas; Tot, total participants. Note: Weights where present are from Fixed effects meta-analysis though Random-effects estimates were identical. Tau^2=0% for all meta-analyses

Seck *et al* was an extended follow-up of this study and this would have led to double counting of patients. Meta-analysis showed that, compared to sulfonylureas, treatment with sitagliptin produced a similar glycaemic change, as measured by reductions in HbA1c from baseline: (weighted mean difference (WMD) in HbA1c 0.05%; 95% CI −0.03% to 0.12%; I^2=0%)) (graph in HbA1c units of mmol/mol is included in online supplementary figure S1). The odds of achieving a HbA1c of <7% by study end was also meta-analysed across these three RCTs, and no significant difference was observed between sitagliptin and sulfonylureas (OR 0.98 95%; CI 0.85 to 1.13, I^2=0%) (figure 2D). Only in the shorter 4.5-month RCT study led by Srivastava, not included in meta-analysis, were sulfonylureas shown to be superior (mean difference (MD) in HbA1c 0.54%; 95% CI 0.43% to 0.64%).

Glycaemic change was also reported in the observational study led by Suraj *et al* (MD 0.49%; 95% CI 0.19% to 0.79%) where a significantly greater reduction in HbA1c was observed with sulfonylureas (figure 2A). Derosa *et al* reported change from baseline in HbA1c after 5 years in a prospective cohort study; however, they did not undertake any formal analysis to adjust for relevant confounders, which made results difficult to interpret, and we have not presented them.

Weight change

Meta-analysis of the three RCTs that could be pooled showed statistically significant reduction in weight with sitagliptin from baseline compared to sulfonylureas (WMD −2.05 kg; 95% CI −2.38 to −1.71 kg; I^2=0%) (figure 2B). This equated to a modest weight increase of approximately 1 kg with sulfonylureas and loss of 1 kg with sitagliptin. Treatment with sitagliptin also showed significant reduction in weight in the remaining RCTs as shown in figure 2B. The greatest comparative weight reduction was observed in the 12-month RCT led by Nauck *et al* (MD −2.60 kg; 95% CI −3.31 to −1.89 kg).

The prospective cohort study led by Suraj *et al* also revealed a similar weight reduction as the RCTs[38]; however, the cohort study led by Valensi *et al* did not find this reduction to be significant with a longer 36-month follow-up (figure 2B).[39]

Changes in body mass index were also reported in a small number of studies, and as results, necessarily, mirror weight change, they have been included in appendix for reference (online supplementary figure S2).

Fasting plasma glucose

Meta-analysis of the three RCTs showed that, compared to sulfonylureas, treatment with sitagliptin produced similar change in fasting plasma glucose (mmol/l) from baseline (WMD 0.11 mmol/L 95%; CI −0.08 to 0.29 mmol/L; I^2=0%) (figure 2C). Of the remaining RCTs, only the shorter 4.5-month RCT study led by Srivastava *et al* demonstrated a more significant reduction in fasting plasma glucose with sulfonylureas (MD 0.81 mmol/l %; 95% CI 0.70 to 0.92 mmol/L).

The observational study led by Suraj *et al* also demonstrated a more significant reduction in fasting plasma glucose with sulfonylureas compared to sitagliptin (MD 1.02 mmol/L; 95% CI 0.52 to 1.52 mmol/L).[38]

Blood pressure and lipid changes

Two RCTs reported no significant difference between sitagliptin and sulfonylureas for change in systolic and diastolic blood pressure, level of triglycerides and cholesterol between study end and baseline (figure 3A–D).

In the RCT led by Ahren *et al*, a clinically insignificant but statistically significant reduction in total cholesterol was observed with sitagliptin compared to sulfonylureas (MD −0.16 mmol/mol; 95% CI −0.29 to −0.03 mmol/mol).[28]

Longer-term outcomes

Two non-randomised studies reported outcomes from longer follow-up of patients not reported in any RCTs retrieved. The 36-month cohort study led by Valensi *et al* explored the risk of needing treatment change after add-on of sitagliptin compared to sulfonylureas (figure 3E).[39] They found that the adjusted risk of needing treatment change was lower with sitagliptin (HR 0.65; 95% CI 0.57 to 0.73).

The 72-month cohort study led by Inzucchi *et al* demonstrated that individuals prescribed sitagliptin had a lower risk for initiating insulin during follow-up after relevant adjustment (HR 0.76; 95% CI 0.65 to 0.90) (figure 3F).[36]

DISCUSSION

In this systematic review, the meta-analysis conducted using three RCTs in which follow-up was greater than 6 months demonstrated similar glycaemic improvement after add-on of sitagliptin compared to sulfonylureas in individuals inadequately controlled on metformin. Statistically significant reduction in weight of approximately 2 kg was observed with sitagliptin when compared to sulfonylureas driven by modest weight increase with sulfonylureas and modest decrease with sitagliptin. This may not be of clinical significance for most individuals other than those at more extremes of weight, for example, frail elderly patients or those struggling to lose weight. Outcome reporting for change in blood pressure and lipids from baseline was low, and meta-analysis was not possible, although data from two RCTs did not show any clinically meaningful difference between both add-on treatments. Two cohort studies reported longer-term outcomes, relating to time before a treatment change or insulin initiation was needed. In both of these high-quality non-randomised studies, results suggested that fewer individuals prescribed sitagliptin than sulfonylureas needed treatment change at 36-month and 72-month follow-ups, respectively.

Meta-analysis of high-quality homogenous RCTs represents the highest source of evidence,[40] and we identified three homogenous RCTs for meta-analysis. However,

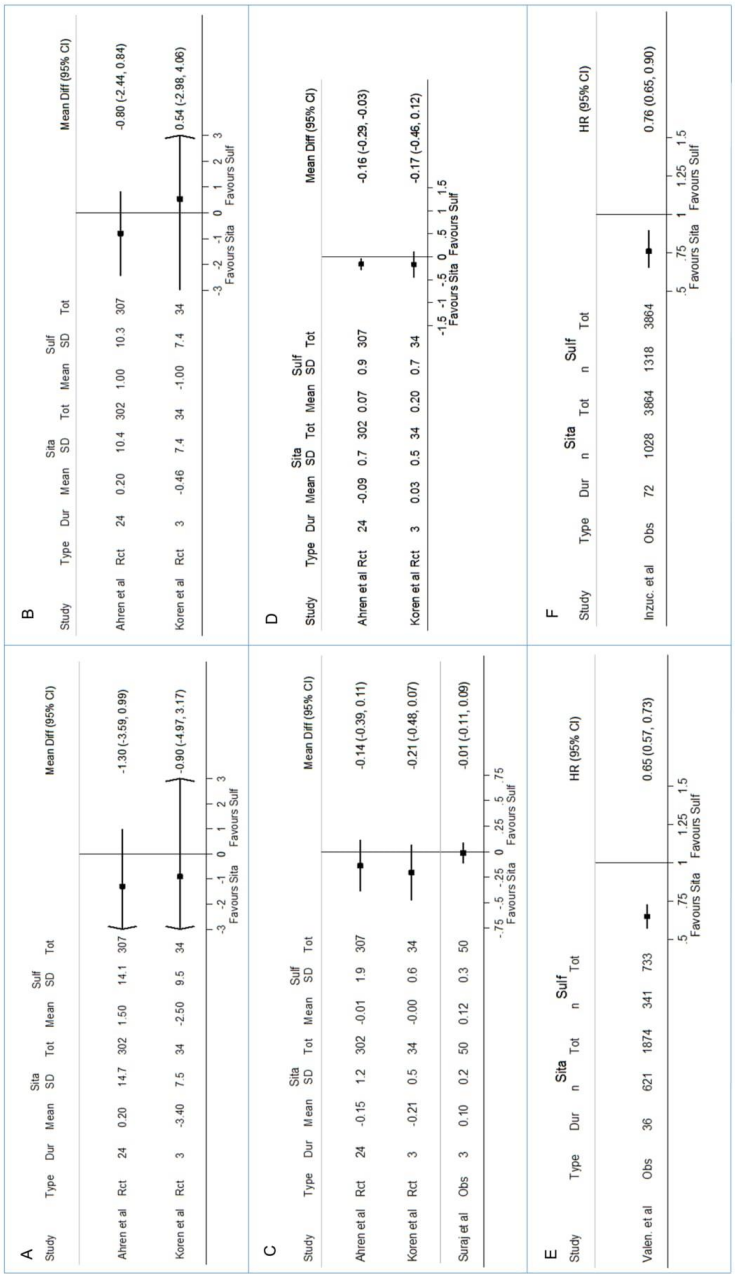

Figure 3 Forest plots comparing sitagliptin and sulfonylureas for change from baseline for systolic blood pressure (mm Hg) (A), diastolic blood pressure (mm Hg) (B), triglycerides (mmol/l) (C), total cholesterol (mmol/mol) (D), risk of needing treatment change (E) and risk of initiating insulin (F). Dur, duration in months; HR, hazard ratio; Mean Diff, mean difference; Obs, non-randomised observational study; Rct, randomised controlled trial; SD, standard deviation; Sita, sitagliptin; Sulf, sulfonylureas.

the RCT inclusion criterias may have led to exclusion of important population subgroups frequently seen in clinical practice decreasing external validity of the findings from the meta-analysis alone. For example, Arechavaleta *et al* excluded individuals with a baseline HbA1c >9%,[29] and Seck *et al* excluded individuals >78 years of age.[33] Drug utilisation studies have shown that such criteria alone can exclude close to 50% of individuals seen in real-world clinical practice.[41] Therefore, by assessing and reporting on the quality of the remaining clinical trials that could not be meta-analysed (some of which had more pragmatic inclusion criteria[31]) and including non-randomised studies that provide insight into effectiveness in actual clinical practice and longer-term outcomes, we believe this study was made more informative.

Glycaemic control achieved with sitagliptin or sulfonylureas in patients inadequately controlled on metformin was similar in our meta-analysis. Synergistic improvement in glycaemic effectiveness has been reported when sitagliptin and metformin are used together; however,[42] our study has shown that the glycaemic reduction results are similar to that achieved when metformin and sulfonylureas are used together. One RCT[34] and cohort study reported significant reductions in HbA1c and fasting glucose with sulfonylureas compared to sitagliptin; however, these were both of 4.5 months in duration only.[38] This peak in sulfonylurea glycaemic efficacy within the first 6 months of treatment has been previously described.[43 44] For all studies of greater than 6-month duration, we found that glycaemic benefit with sitagliptin and sulfonylurea was comparable in line with guidance from major international bodies.[1–4 9]

Statistically significant weight loss with sitagliptin compared to sulfonylurea of approximately 2 kg was evident in our meta-analysis and also across all RCTs and non-randomised studies reported up to 2 years in duration. This difference was driven by modest weight decrease with sitagliptin and increase with sulfonylureas. Sitagliptin is often described as having only a weight neutral effect[45–47]; however, when compared directly with sulfonylureas, a small reduction in weight is evident. This comparative reduction is unlikely to be clinically significant for most individuals other than those at more extremes of weight or those struggling to lose weight.

Longer-term outcomes with follow-up greater than 2 years were reported in two cohort studies only.[36 39] The risk of requiring a change in treatment or initiating insulin was found to be lower with sitagliptin, suggesting that sitagliptin patients are less likely to need treatment change over longer follow-up. However, decisions to change treatment or initiate insulin are based on clinician decisions, which can be subjective and hence vary. Furthermore, treatment inertia is a well-established problem in care of individuals with type 2 diabetes.[48] Without data on glycaemic control at the time of treatment change, we cannot fully assess whether clinicians changed treatment appropriately, making this finding challenging to interpret.

Only 2 RCTs reported data on markers of cardiovascular disease and these did not show any clinically significant change being achieved in blood pressure or lipids through being prescribed sitagliptin or sulfonylureas as add-on to metformin. Cardiovascular outcome studies comparing sitagliptin to placebo have also been conducted recently[49]; however, direct comparisons between a DPP-4 inhibitor and sulfonylurea will not emerge until 2019 on completion of the CAROLINA study.[50] This study will focus on use of linagliptin rather than sitagliptin, which raises a challenge as recent RCT results for different DPP-4 inhibitors were conflicting, raising the possibility that different DPP-4 inhibitors may exhibit different cardiovascular risks.[49 51 52] Equally, the effect of sulfonylureas on cardiovascular disease is still poorly understood despite many years of usage.[53 54] Studies have reported increased mortality from cardiovascular disease with use of sulfonylureas particularly tolbutamide and chlorpropamide[43 55]; however, results from more recent RCTs with newer sulfonylureas like gliclazide are more reassuring.[43 56] Further research is needed.

No RCTs or non-randomised studies reported longer-term data on the risk of complications of diabetes such as retinopathy, neuropathy and nephropathy despite these being well established as consequences of poor longer-term glycaemic control.[22] A comparative effectiveness pragmatic clinical trial, the Glycemia Reduction Approaches in Diabetes, is underway that will compare sitagliptin with sulfonylureas in individuals with T2DM inadequately controlled on metformin for longer-term complications.[57] However, the results of this trial are not expected until 2020, and this evidence is needed urgently. Mounting observational data could help investigate these outcomes.

Strengths and limitations

Our study has some important strengths. This is the first systematic review, to our knowledge, to assess effectiveness from both RCTs and non-randomised studies comparing sitagliptin with sulfonylureas as add-on to metformin. Secondly, we have reported data across a wide range of outcomes, and thirdly, we have undertaken meta-analysis only where methodologically appropriate in accordance with our prespecified protocol.[21]

There are also some limitations to acknowledge. Firstly, we have focused entirely on effectiveness in this review because safety has been evaluated in-depth elsewhere as summarised earlier.[8 11 12 15 58] Secondly, we have presented intention-to-treat results (where available) from each study reported. Though this can bias results towards equivalence if there are high dropout rates or considerable switching in studies, this was not the case across studies included. Moreover, our goal was to shed further light on the effectiveness of sitagliptin compared to sulfonylureas with a focus on the initial prescribing decision, and this was the most informative approach to achieve this. Thirdly, our analysis has focused on sitagliptin only as it has been the most extensively prescribed DPP-4 inhibitor

in the UK and USA.[7] Different sulfonylureas do exhibit different pharmacokinetic behaviour, particularly with regards to duration of action; however, they have been grouped together because included studies used mainly newer generation sulfonylureas, which from a pharmacodynamic effectiveness point of view, behave similarly.[43] Finally, despite high prevalence of type 2 diabetes in Asia, no study based solely within an Asian country qualified for the meta-analysis. This omission is of significance as evidence is emerging that suggests that glycaemic effectiveness of DPP-4 inhibitors like sitagliptin may in fact be greater in East Asians. This may be due to phenotypic variation in diabetes and highlights why further research may be needed to identify Asian ethnic subgroups who may need different therapeutic approaches.[59]

CONCLUSIONS

In summary, the absence of data on effectiveness comparing sitagliptin with sulfonylureas among individuals with T2DM inadequately controlled on metformin for reducing longer-term complications of T2DM means treatments decisions for effectiveness (once safety has been considered) must be based on short-term to medium-term outcome data available. In this respect, we have shown that glycaemic control with both treatments was similar. Statistically significant weight reduction of close to 2 kg was observed with use of sitagliptin when compared to sulfonylureas in both RCTs and non-randomised studies, though this may not be of major clinical importance for most individuals. Non-randomised studies also reported that there was a lower likelihood of treatment change after initiation of sitagliptin compared to sulfonylureas. However, it was difficult to interpret if this was necessarily a positive finding due to lack of glycaemic data at time of treatment change. Further comparative effectiveness research work is needed from RCTs or non-randomised studies to address evidence gaps relating to risks of longer-term macrovascular and microvascular complications of T2DM.

Contributors MS, IN and IP collectively planned the study. MS drafted both the systematic review protocol and manuscript. MS and NB assessed eligibility of included articles, extracted data and assessed quality of the studies. IN and IP served as adjudicators for disagreements. MS performed the analysis and with NB, IN and IP interpreted the results. MS, NB, IN and IP all reviewed the manuscript for intellectual content and approved the final version.

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