Pregestational diabetes mellitus during pregnancy and its adverse effects

This work is presented as a thesis for the degree of

Doctor of Philosophy

At

University College London

By

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2017

Declaration

I, Sonia Jayne Coton, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Signed: _____

Abstract

Background: In 1989 the Saint Vincent declaration set out to reduce the risk for pregnant women with diabetes to those without diabetes. A number of studies, since the declaration found that foetal and neonatal adverse pregnancy outcomes in women with type 1 diabetes remained increased. Literature for women with type 2 diabetes and maternal complications is limited. My aim is to assess whether women with type 1 and 2 diabetes remain at increased risk of pregnancy complications.

Methods: Using a primary care database; THIN, I investigated the prevalence of: pregestational diabetes in pregnancy and pregnancy complications. Finally, I examined the risk of pregnancy complications for women with diabetes in pregnancy compared to women without diabetes in pregnancy.

Results: The prevalence of type 1 diabetes pregnancy increased from 1.58 to 4.34 per 1,000 pregnancies between 1995 and 2012. The prevalence of type 2 diabetes in pregnancy steadily increased from 2.38 to 4.83 per 1,000 pregnancies between 1995 and 2008; then increased more rapidly until the end of the study period to 10.37 per 1,000 pregnancies in 2012.

Women with type 1 diabetes remained at increased risk of caesarean section (RR 2.41 (2.13, 2.72)) and major congenital malformations (RR 2.29 (1.53, 4.85)) compared to women without diabetes after adjusting for maternal characteristics. Women with type 2 diabetes remained at increased risk of caesarean section (RR 1.58 (1.42, 1.75) and perinatal death (RR 2.72 (1.53, 4.85)) when compared to women without diabetes after adjusting for maternal characteristics.

Conclusion: Women with type 1 and type 2 diabetes remained at increased risk of experiencing pregnancy complications. There is still substantial work to be done to reduce the adverse outcomes experienced by women with diabetes in pregnancy and meet the recommendations set out in the Saint Vincent declaration nearly thirty years ago.

Acknowledgements

Firstly, I would like to thank my supervisors Dr Irene Petersen and Professor Irwin Nazareth for their invaluable ideas and guidance over the course of my PhD. Their continual support made my time as a PhD student far more enjoyable.

To the NIHR School for Primary Care Research, thank you for funding my research through a pre-doctoral studentship.

Thank you to all THIN team members, past and present, that I have had the pleasure of working with over the past three years. I would like to thank you all for sharing your expertise, insight, and support so generously. I would also like to thank Tra Pham, Ann Liljas, Manuj Sharma, and Shuk-Li Collins for kindly volunteering to proof read for me.

To my friends and family, thank you for your unwavering support and understanding while I have been carrying out this work.

Finally, to my husband Jack thank you for your unconditional love and support.

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List of abbreviations

ACU	-	Acceptable Computer Usage
AHD	-	Additional Health Data
AMR	-	Acceptable Mortality Reporting
BMI	-	Body Mass Index
BNF	-	British National Formulary
BP	-	Blood pressure
CEMACH	-	Confidential Enquiry into Maternal and Child Health
CI	-	Confidence Interval
CPRD	-	Clinical Practice Research Datalink
DKA	-	Diabetic ketoacidosis
EUROCAT	-	European surveillance of congenital anomalies
GLP-1	-	Glucagon-like peptide-1
GMC	-	General medical council
GP	-	General Practitioners

GPRD	-	General Practice Research Database
HbA1c	-	Glycated Haemoglobin
HSCIC	-	Health and Social Care Information Centre
MBRRACE-UK	-	Mothers and Babies: Reducing Risk through Audits and Confidential Enquires across the UK
MCM	-	Major Congenital malformations
NHS	-	National health service
NICE	-	National Institute of Clinical Excellence
NorDip	-	Northern Diabetic Pregnancy Survey
OAD	-	Oral antidiabetic
ONS	-	Office of National Statistics
PCOS	-	Polycystic ovary syndrome
PIH	-	Pregnancy induced hypertension
SD	-	Standard deviation
SMR	-	Standardized Mortality Ratio
T1	-	Type 1 diabetes

T2	-	Type 2 diabetes
THIN	-	The Health Improvement Network
UK	-	United Kingdom
WHO	-	World Health Organization

Chapter 1 Introduction

1.1 Diabetes mellitus

Diabetes mellitus is a chronic metabolic condition affecting the body's ability to regulate the level of glucose in the blood with disturbances in carbohydrate, protein, and fat metabolism. In non-diabetics, two hormones: insulin, and glucagon; are produced in the pancreas islet cells to regulate glucose homeostasis. Insulin is produced in the beta cells of the pancreas when levels of blood glucose rise. In response to insulin, cells take up more glucose and liver cells store glucose as glycogen. When blood glucose levels fall, glucagon is produced in the alpha cells of the pancreas and the liver cells convert the stored glycogen back to glucose. In people with diabetes, insulin secretion, insulin action or both are impaired, resulting in high levels (hyperglycaemia) and low levels (hypoglycaemia) of blood glucose, which, if left untreated, can become life threatening (see Section 1.1.5 below for details of diabetic complications).

Diabetes affects approximately 382 million people worldwide (1). It is estimated that one in 20 people in the United Kingdom (UK) has diabetes (diagnosed or undiagnosed) (2). The prevalence of diabetes is increasing globally. In the UK, over a 10 year period, the prevalence of diabetes increased 54% in the general population, from 2.8% in 1996 to 4.3% in 2005 (3).

There are two main types of diabetes: type 1 diabetes mellitus, and type 2 diabetes mellitus; type 1 diabetes accounts for 10% of UK diabetics (4). Another sub-type of diabetes mellitus is gestational diabetes, which is diabetes with first occurrence during pregnancy, with or without resolution after delivery. All women experience some level of insulin resistance during pregnancy to allow the baby to develop. Insulin resistance occurs when the body fails to react to insulin as it should. In women with gestational diabetes, the insulin resistance increases to a point where the body is no longer able to produce enough insulin resulting in blood glucose levels remaining dangerously high (hyperglycaemic) which can have negative effects on the foetus. Although, gestational diabetes is a sub-type of diabetes only type 1 and type 2 diabetes will be studied in this thesis.

The following section will provide an overview of type 1 and type 2 diabetes and the potential treatments, as well as comorbidities associated with diabetes in the general

population. The second section of this chapter is a description of diabetes in pregnancy and the associated complications.

1.1.1 Type 1 diabetes mellitus

Type 1 diabetes mellitus is caused by an autoimmune response that destroys the beta cells in the pancreas resulting in little or no insulin secretion. As such, after diagnosis insulin must routinely be injected into the body for the long term.

Type 1 diabetes usually occurs in non-overweight, white, children or adolescences in the presence of rapidly occurring severe symptoms of hyperglycaemia. Five to ten percent of people with type 1 diabetes present with diabetic ketoacidosis (DKA) (5). DKA is a life-threatening condition where the body breaks down fat as an alternative to glucose, due to a lack of insulin, resulting in toxic levels of ketones in the blood. Peak incidence of type 1 diabetes diagnosis is between the ages of ten and 15 years old (6).

Former obsolete terms used for type 1 diabetes are: insulin dependent, juvenile-onset, or ketosis-prone diabetes.

1.1.2 Type 2 diabetes mellitus

Type 2 diabetes mellitus is caused by a reduction in insulin secretion and a decrease in insulin activity. For a period after diagnosis, type 2 diabetes may be controlled by diet and weight loss alone, but type 2 diabetes is a progressive condition and, as insulin secretion and sensitivity decrease, treatment may progress to oral antidiabetic therapies and/or insulin injections.

Type 2 diabetes is usually diagnosed in overweight adults with a strong family history of the condition; although not all people with type 2 diabetes will be overweight. Type 2 diabetes is increasingly prevalent among black and Asian ethnic groups (7). Symptoms of hyperglycaemia often occur over a long period of time and tend to be less severe than in those with type 1 diabetes (5). Approximately 50% of type 2 diabetics in the UK are undiagnosed because symptoms of hyperglycaemia are not recognised or are mild (5). Twenty percent of type 2 diabetics are already experiencing diabetic complications when they are diagnosed due to the delay between disease onset, recognition, and diagnosis (6).

Former obsolete terms used for type 2 diabetes are: non-insulin dependent, maturity onset, or non-ketosis-prone diabetes.

1.1.3 Diagnosing diabetes mellitus

People with diabetes will present with a mixture of hyperglycaemia symptoms and will have increased blood glucose concentration upon testing. Hyperglycaemic symptoms include: increased thirst (polydipsia), increased urine production (polyuria), unexplained weight loss, fatigue, blurred vision, and recurrent or severe infections. As outlined earlier, symptoms usually occur very rapidly in individuals with type 1 diabetes, whereas individuals with type 2 diabetes can have no symptoms or not notice their symptoms as they develop very slowly over a number of years (5).

For both type 1 and type 2 diabetes diagnosis is made by identifying abnormally high blood glucose via testing. The National Institute for Health and Clinical Excellence (NICE) use the World Health Organization (WHO) 2006 recommendations to diagnosis diabetes (8–10). In people with mild or no symptoms of hyperglycaemia, two raised blood glucose tests on separate days are necessary to confirm a diabetes diagnosis. For people with clinical symptoms of hyperglycaemia, a single raised blood glucose test is sufficient to confirm a diabetes diagnosis.

The 2006 WHO report, “Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia” (8) criteria for diagnosing diabetes is:

- fasting plasma glucose ≥ 7.0mmol/L (126 mg/dl),
- or 2 hour plasma glucose ≥ 11.1mmol/L (200mg/dl) following a 75g glucose drink,
- or random plasma glucose ≥ 11.1mmol/L (200mg/dl)

Tests should not be carried out if the person is ill or stressed as this may affect the results. If results are different on repeated tests, re-testing after an interval is recommended.

In 2011, the WHO updated their diagnostic criteria to include the use of glycosylated haemoglobin (HbA_{1c}) for diagnostic testing (11). HbA_{1c} reflects the average plasma glucose over the previous 8 to 12 weeks. HbA_{1c} may be preferable to fasting or oral glucose tolerance testing as it provides an insight into an individual’s glucose control over the previous 8 to 12 weeks instead of a snapshot in time and does not require the

individual to fast beforehand. HbA_{1c} concentrations of 6.5% (48 mmol/mol) and above confirm a diabetes diagnosis.

1.1.3.1 Diagnosing diabetes mellitus in pregnancy

HbA_{1c} is used outside of pregnancy for diagnosing and monitoring of diabetes but, it is affected by pregnancy and may not be a reliable tool for diagnosing gestational diabetes or monitoring diabetes control during pregnancy. A study on pregnant women without diabetes found that HbA_{1c} levels are lower in early and late pregnancy (12), indicating that pregnancy specific diagnostic thresholds for HbA_{1c} may need to be developed (13). NICE do not recommend using HbA_{1c} to routinely assess a woman's diabetes control during pregnancy (7).

1.1.4 Treating diabetes mellitus

The aim of treatment for diabetes is to regain control of blood glucose levels so that the potentially life threatening immediate effects of hyperglycaemia and risk of long-term complications are minimised. The long term complications of hyperglycaemia are outlined in Section 1.1.5 below. An individual with diabetes should aim to keep their blood glucose levels as near to normal as possible; this entails good diabetic control. NICE recommends maintaining HbA_{1c} below 7.5% with minimal hypoglycaemic incidents (9,10).

1.1.4.1 Insulin treatment

Insulin is used by diabetics as a hormone replacement treatment, with the purpose of mimicking the insulin secretion of a person without diabetes (5). Insulin is deactivated by the gastro-intestinal enzymes in the body and therefore must be given by injection, usually subcutaneously. Injection sites must be rotated routinely to reduce the risk of insulin reactions such as: allergy, lipohypertrophy, and lipoatrophy (5,14). Lipohypertrophy (the accumulation of fatty deposits under the skin) is common among insulin using diabetics that repeatedly use the same area to inject and causes erratic absorption of insulin. Allergy and lipoatrophy (the loss of subcutaneous fat) are rare adverse events associated with insulin use (5).

There are several different forms of insulin available: animal, human, and analogue. Animal insulin is extracted from porcine and bovine pancreas and purified, whereas human insulin is semi-synthetically produced (14). Analogue insulin is a subtype of human insulin and is engineered to act more rapidly or uniformly (14).

The type of insulin regime prescribed to a person with diabetes depends on a number of things: age, weight, how often they intent to check their bloods, and an element of trial and error. There are three main types of insulin preparation: short acting, intermediate acting, and long acting.

Short acting insulin includes soluble and rapid acting analogue insulin. Soluble insulin is effective between 30 to 60 minutes after injection and is active up to eight hours afterwards. Rapid acting analogue insulin has been modified to be effective straight away; it is effective between five to 15 minutes after injection and is active up to four hours afterwards. Intermediate and long acting insulins are modified to reduce solubility. They are effective one-two hours after injection and continue to work for up to 16-35 hours (14).

Pre-mixed insulins are available which contain both short acting and intermediate or long acting insulins. There are problems with pre-mixed regimes as they are inflexible; neither the short nor longer acting insulins can be increased without also increasing the other. To remove this difficultly regimes of short acting and longer acting insulins can be prescribed separately.

Examples of insulin regimes are (14):

- Short-acting insulin mixed with intermediate acting insulin: twice daily (before meals)
- Short acting insulin mixed with intermediate acting insulin: before breakfast. Short acting insulin: before evening meal and intermediate acting insulin: before bedtime
- Short acting insulin: three times a day (before breakfast, midday, and evening meals) and intermediate acting insulin: at bedtime

1.1.4.2 Oral antidiabetic treatment

Oral antidiabetic treatments are primarily used to control the concentration of blood glucose in individuals with type 2 diabetes (14). They are introduced as a treatment regime after the introduction of a controlled diet and lifestyle changes have failed to adequately control blood glucose concentrations or after the progression of their diabetes. The available treatments work in a number of ways, either by increasing insulin secretion, increasing peripheral insulin uptake, or delaying glucose absorption. Oral antidiabetics can be grouped into: biguanides, sulphonylureas, and other antidiabetic drugs.

Metformin, the only available biguanide, is the first line of defence for overweight type 2 diabetics after the progression of diabetes. It increases peripheral utilisation of glucose and supresses gluconeogenesis (the generation of glucose from non-carbohydrates) (6). Metformin can be prescribed alone or in combination with insulin or other oral antidiabetics. Side-effects include nausea, vomiting, diarrhoea, abdominal discomfort, and very rarely lactic acidosis. Hypoglycaemic incidents are rare with metformin (14).

Sulphonylureas increase insulin secretion and therefore only work in type 2 diabetics with some remaining insulin production. Sulphonylureas should be considered for use in people that are not overweight and have intolerance or contra-indications against metformin. Sulphonylureas can be used in combination with insulin or other oral antidiabetics. Side-effects include weight gain, nausea, vomiting, diarrhoea, constipation, disturbances in liver function, and hypoglycaemia (14).

Other antidiabetic treatments include: meglitinides, thiazolidinediones, glucagon-like peptide-1 agonists, and alpha glucosidase inhibitors.

Meglitinides, like sulphonylureas, increase insulin secretion but have a more rapid onset and a shorter duration of activity. Side-effects include weight gain, gastrointestinal disturbances, and hypoglycaemia (14).

Thiazolidinediones reduce peripheral insulin resistance to decrease blood glucose concentrations. Side-effects include weight gain, gastrointestinal disturbances, oedema, anaemia, hypoglycaemia, and fractures. Thiazolidinediones cannot be used in people with a history of heart failure (14,15).

Glucagon-like peptide-1 (GLP-1) agonists mimic the hormone GLP-1 activity; it increases insulin secretion, slows gastric emptying, and supresses' glucagon secretion. Side-effects include gastrointestinal disturbances, and hypoglycaemia. GLP-1 agonists may encourage weight loss (14).

Alpha glucosidase inhibitors inhibit enzymes that release glucose from complex carbohydrates. This results in a delay in the digestion and absorption of glucose. Side-effects include flatulence, diarrhoea and stomach discomfort (14).

For some individuals with type 2 diabetes oral antidiabetics alone may not adequately control concentrations of blood glucose. In these cases it is necessary to use insulin in addition or as a substitute for the oral antidiabetics.

1.1.4.3 Diet and lifestyle

Management of diabetes cannot be achieved without an appropriate diet. NICE do not provide specific guidelines for diet and lifestyle plans among people with diabetes. Instead, all newly diagnosed diabetics should receive individual advice from a dietician to provide tailored changes to their diet. General recommendations for a healthy balanced diet are: eat three meals spread at regular intervals throughout the day; each meal should include high-fibre and low glycaemic index foods (such as whole grains, legumes or brown rice); eat plenty of whole fruit and vegetables; substitute animal products high in cholesterol and saturated fat with lean meats, fish and poultry; and quench thirst with water. Recommendations also cover substituting snacks high in sugar and saturated fat for nuts or fruit, and using low-fat dairy alternatives (5,6,16). A healthy balanced diet will provide sufficient energy for everyday activities without causing weight gain.

Type 2 diabetics are frequently overweight or obese when diagnosed. Changing dietary habits to that of a healthy balanced diet are recommended to, prevent further weight gain, and encourage weight loss, as well as to manage their diabetes.

In addition to changes to their diet, newly diagnosed diabetics are encouraged to give up smoking, take moderate exercise, and limit the amount of alcohol they drink (16,17).

1.1.4.4 Treating diabetes mellitus during pregnancy

The management and treatment of diabetes during pregnancy starts with preconception care provided by the woman's GP. Women with diabetes that are planning on becoming pregnant are advised to avoid pregnancy until they can maintain good blood glucose control; HbA_{1c} below 48 mmol/mol (6.5%) (18). A medication review will also be conducted. Metformin is the only oral antidiabetic medication that is advised during pregnancy (unlicensed use); all other oral antidiabetics should be discontinued and insulin substituted (18).

1.1.5 Diabetic complications

Diabetic complications are associated with periods of hyperglycaemia and hypoglycaemia. Hyperglycaemia is defined as fasting blood glucose levels greater than 7.0mmol/L (8) and can lead to damage of the nerves, blood vessels, and organs (19). Even relatively moderate increases in blood glucose can have severe long term

consequences, which is why it is important for people with diabetes to maintain good control of their blood glucose levels.

Complications due to long term hyperglycaemia can be divided into microvascular and macrovascular complications (19). Microvascular complications are caused by damage to the small blood vessels and include: diabetic nephropathy (kidney disease), neuropathy (nerve damage), and retinopathy (eye disease) (6,15,16,19). Diabetic neuropathy is probably the most common diabetic complication, being present in 30% to 40% of type 1 diabetes and type 2 diabetes individuals (4).

Macrovascular complications are caused by atherosclerosis, which leads to narrowing of the arterial walls. Macrovascular complications include: coronary artery disease, peripheral vascular disease, and stroke (19). Further, diabetic neuropathy and peripheral vascular disease are risk factors for diabetic foot complications. The loss of sensation and pain caused by diabetic neuropathy and peripheral vascular disease result in people with diabetes not noticing injuries to their feet leading to infection, ulcers, and in severe cases amputation (20,21).

Diabetic ketoacidosis is a consequence of severe short term hyperglycaemia. Without quick and effective treatment, diabetic ketoacidosis can lead to death and therefore should be treated as a medical emergency (22). Diabetic ketoacidosis is caused by insulin deficiency leading to the body using fat as an energy source instead of glucose (23). This results in ketones, a waste product from fat metabolism, building up in the blood eventually rising to a toxic level, resulting in ketoacidosis. Clinical features include: increased thirst and polyuria, weight loss, weakness, blurred vision, laboured respiration, abdominal pain, leg cramps, nausea and vomiting, confusion, and drowsiness (24). Diabetic ketoacidosis is treated immediately with a combination of insulin and fluids (24). Another key area of treatment is to identify the underlying cause of hyperglycaemia and the resulting diabetic ketoacidosis event; this could be poor adherence to insulin treatment, infection or initial presentation of diabetes.

Another source of diabetic complication is hypoglycaemia. Hypoglycaemia is defined as blood glucose level less than 3.5mmol/L (25) and is an adverse side effect of treatment for diabetes, and is mainly experienced by diabetics using insulin or sulphonylureas (26). Short term effects of hypoglycaemia include: cognitive impairment, increased risk of accidents, increased risk of fractures, and in severe cases, coma, and seizures (26). Hypoglycaemia can also have long term effects, mainly due to the fear of another

hypoglycaemic event leading to a loss of diabetes control, resulting in hyperglycaemia, and complications related to hyperglycaemic periods (26,27).

1.2 Diabetes mellitus during pregnancy

Diabetes mellitus is one of the most common chronic pregestational conditions affecting pregnancies in the UK (28). In 2007, diabetes affected 1 in 250 of pregnancies in England, Wales and Northern Ireland each year (29). Before the introduction of insulin, few women with diabetes became pregnant, and infertility for women with diabetes was the norm. After the introduction of insulin in the early 1920s the prevalence of diabetes in pregnancy increased (30). In 2008, type 1 diabetes accounted for 7.5% of all diabetic pregnancies in England and Wales with type 2 diabetes accounting for 5%; the remaining 87.5% of diabetic pregnancies were affected by gestational diabetes (7).

Pregnancy, even in non-diabetic women, results in increasing insulin resistance as the pregnancy progresses due to the placental hormones. For diabetic women, this leads to the need of increased medication to control hyperglycaemia. Diabetes can adversely affect pregnancy at any stage from fertilisation to delivery and beyond, but hyperglycaemia during the preconception and organogenesis periods probably have the largest effect on foetal alterations (31). Adverse pregnancy outcomes due to diabetes in pregnancy have been linked to poor glycaemic control during pregnancy. To reduce the risk of pregnancy complications women with diabetes are advised to maintain tight control of their blood glucose concentrations throughout the pregnancy (31).

The prevalence of diabetes is rising worldwide and has increased in the UK over recent years (2,3,32,33). This general population increase is also reflected in an increase in the prevalence of pregestational diabetes in pregnancy. In under a decade, the prevalence of pregnancies affected by pregestational diabetes rose from 3.1 per 1,000 births in 1996-98 to 4.7 per 1,000 births in 2002-04, just over a 50% increase (34).

1.2.1 Complications due to diabetes mellitus in pregnancy

Women with diabetes are at increased risk of adverse pregnancy outcomes when compared to women without diabetes in pregnancy. Adverse pregnancy outcomes can be divided into adverse events for the mother and adverse events for the foetus. Examples of maternal adverse pregnancy outcomes include: hypertension, preeclampsia, spontaneous preterm labour, still birth, miscarriage, and caesarean

section (31,35). Examples of foetal adverse outcomes include: excessive foetal growth (macrosomia), birth injury or trauma, neonatal hypoglycaemia, respiratory distress syndrome, and congenital malformations (31,35).

Women with diabetes can also experience complications of diabetes due to pregnancy. Diabetic complications due to pregnancy include: worsening of pre-existing diabetic retinopathy, nephropathy, and neuropathy, and altered glycaemic control resulting in periods of hypoglycaemia and hyperglycaemia (31,35). Placental hormones increase as the pregnancy progresses, increasing the level of insulin resistance. If hyperglycaemic events are not controlled, changes to diabetic treatment may be introduced to maintain glycaemic control. Changes to treatment can include: switching therapies, increased dose, changing from contra-indicated therapies, and the addition of new therapies (14).

Pregnant women with diabetes have more frequent appointments and scans than pregnant women without diabetes. After the first contact with a healthcare professional, all pregnant women will be sent for a booking appointment before the 10th week of pregnancy and offered at least two ultrasound scans (36). The first scan usually occurs between the 8th and 14th weeks of pregnancy and the second takes place between the 18th and 20th weeks of pregnancy. Pregnant women will also see a midwife or doctor at 28, 34, 36 weeks gestation (36). In addition to these usual appointments, pregnant women with diabetes will have appointments at: 16-20 weeks for retinal assessment for women with signs of diabetic retinopathy during the booking appointment; 18-20 weeks for four-chamber view of foetal heart; 28, 32 and 36 weeks gestation for ultrasounds to assess foetal growth and amniotic fluid volume; weekly appointments from 38 weeks gestation until the end of pregnancy for foetal wellbeing tests and, if necessary induction of labour or caesarean section delivery (7).

1.3 The Saint Vincent declaration

In 1989 representatives from all European governments met with diabetes specialists, the World Health Organization (WHO), and the International Diabetes Federation in Saint Vincent, Italy, to develop goals for tackling the growing health problem with diabetes (37). At the closure of the St Vincent meeting, those present agreed on a set of recommendations to implement in their home countries. The recommendations included five goals to reduce the impact of diabetes on the population in terms of awareness, diagnosis, treatment of diabetes, and prevention of diabetic complications.

The five goals of the St Vincent declaration were (37):

1. Reduce new blindness due to diabetes by one third or more.
2. Reduce numbers of people entering end-stage diabetic renal failure by at least one third.
3. Reduce by one half the rate of limb amputations for diabetic gangrene.
4. Cut morbidity and mortality from coronary heart disease in the diabetic by vigorous programmes of risk factor reduction.
5. Achieve pregnancy outcome in the diabetic woman that approximates that of the non-diabetic woman.

Since the declaration in the 1989 there have been two updates. The first occurred in Istanbul on the tenth anniversary of the St Vincent meeting, 1999 (38). At this meeting the lack of implementation following the St Vincent declaration was highlighted and all representatives present reaffirmed their commitment to reducing the burden of diabetes. The second update occurred in Glasgow on the 20th anniversary of the St Vincent declaration meeting, 2009 (39). At both update meetings commitment to the five goals was reaffirmed.

The St Vincent declaration highlighted that diabetes is a growing public health problem and subsequent meetings show diabetes remains to be cause for concern. At the time of the declaration in 1989, at least ten million Europeans were affected by diabetes, by 2005, nearly 20 years after the declaration, the estimate had risen to 31 million (37,40).

The St Vincent declaration highlighted that women with diabetes experience higher rates of adverse pregnancy outcomes than women without diabetes during pregnancy. The aim from the declaration was for women with diabetes in pregnancy to experience similar risks of adverse pregnancy outcomes as women without diabetes in pregnancy (37).

This PhD aims to investigate the risk of certain pregnancy outcomes for women with diabetes compared to women without pregestational diabetes and assess how the risk has changed over time.

1.4 Summary

This chapter discussed what diabetes mellitus is, how it is diagnosed, managed and the possible complications an individual with diabetes might experience. This chapter also

discussed the effect diabetes mellitus has on pregnancy in terms of additional maternal monitoring, maternal and foetal adverse pregnancy outcomes, and how diabetes mellitus treatment and care is affected by pregnancy.

The following chapters will outline the rationale and objectives of this PhD and describe the primary care database that was used during this project.

Chapter 2 Literature review and Rationale

2.1 Introduction

In the previous chapter I defined diabetes and pregestational diabetes and briefly discussed how women with diabetes are generally cared for before and during pregnancy, and the problems they may face during pregnancy. In this chapter I will review the relevant literature.

The complications that women with diabetes in pregnancy may experience can be divided into two groups. The first group contains maternal diabetic complications due to the pregnancy; for example, worsening of pre-existing retinopathy or worsening of blood glucose control. The second group of complications are foetal and maternal adverse pregnancy outcomes due to the woman's diabetic status; such as large for gestational age babies or increased risk of still birth. This thesis will focus on complications in the second group; adverse pregnancy outcomes related to diabetes.

The prevalence of diabetes is increasing and is a growing health problem. In 2000 diabetes affected 382 million people worldwide and is projected to affect 592 million people by 2035 (1,2,41). As the prevalence of diabetes increases in the general population it also increases in the pregnant population (34). The St Vincent declaration in 1989, as described in Section 1.3 of the previous chapter, outlined a set of recommendations to: prevent, identify, and improve treatment of people with diabetes. The fifth recommendation of the St Vincent declaration was to reduce adverse pregnancy outcomes in women with diabetes during pregnancy to correspond to those of women without diabetes in pregnancy (37).

Nearly three decades have passed since the St Vincent declaration, and a number of studies have attempted to determine the effect of the declaration on adverse pregnancy outcomes for women with diabetes in pregnancy (42,43). A review by Colstrup *et al* (42) published in 2013 assessed 12 population based studies with a sample of over 200 women with type 1 diabetes and compared neonatal and foetal outcomes to the background population. They found that women with type 1 diabetes experience an increased risk of: congenital malformations (Risk Ratio 2.4, range (1.5, 6.4)); perinatal mortality (RR 3.7, range (2.8, 9.4)); preterm delivery (RR 4.2, range (2.2, 8.6)); and large

for gestational age (RR 4.5, range not presented)). They concluded that the recommendations of the St Vincent declaration had not been met (42).

I conducted a broad literature review using web of science to evaluate the previous research in terms of pregestational diabetes and the risk of any adverse pregnancy outcome. The limitation with the Colstrup *et al* review, and the broad literature review I conducted, was that it mainly excluded women with type 2 diabetes and focused on adverse outcomes for the baby. Another limitation of the current literature is the sample size and study setting. A lot of studies have small sample sizes and select pregnant women from specialist hospitals or maternity units. Therefore, this PhD will include women with both type 1 and type 2 diabetes and will primarily focus on maternal adverse pregnancy outcomes. The selected adverse outcomes are: caesarean section delivery (including both elective and emergency); instrumental delivery (delivery assisted via ventouse or forceps); pregnancy induced hypertension, preeclampsia and eclampsia; perinatal mortality; and major congenital malformations.

2.2 Narrative literature review

I conducted a narrative literature review using web of science to evaluate the previous research in terms of pregestational diabetes and the risk of the selected adverse maternal and child outcomes. For this review my population of interest was pregnant women, the exposure was pregestational diabetes, and each of the selected outcomes (caesarean section, instrumental delivery, perinatal death, preeclampsia, and major congenital malformations) were independently set as the outcome. The search terms used for each outcome are presented in Appendix I. All papers published in English between the 1st of January 1990 and the 31st of December 2013 were identified and abstracts were screened. Papers examining gestational diabetes and pregnancy in animals were excluded. The reference lists of all relevant publications were also screened to find any additional publications. This process was conducted for each outcome independently.

2.2.1 Caesarean section literature review

Since 1985 the World Health Organization (WHO) considered the ideal rate for caesarean section delivery to be between 10% and 15%, above this rate there is no additional mortality rate benefit for the mother (44). I found eight studies (Table 2.1) examining caesarean section delivery among women with diabetes in pregnancy (45–52).

All but one of the studies was conducted using women drawn from hospital populations (52), only three studies examined women with type 1 and type 2 diabetes in pregnancy (45,47,51), and three studies made no comparisons to either a selected comparison population or national/regional data (46–48). A Swedish study on just over five thousand women with type 1 diabetes and 1.3 million women without diabetes selected from a national registry had a significantly larger sample size than the other studies and found women with type 1 diabetes had over a fivefold increase in the odds of caesarean section compared to non-diabetic women (OR 5.31, 95% CI (4.97, 5.69)) (Table 2.1) (52).

The prevalence of caesarean section delivery among women with diabetes was substantially higher than the WHO recommendations. Among the studies that sampled women with both type 1 and type 2 diabetes the prevalence of caesarean section delivery ranged from 36% (95% CI (24%, 48%)) up to 62% (95% CI (53%, 71%)) (45,47,51). Among the four studies that sampled women with type 1 diabetes and excluded women with type 2 diabetes the prevalence of caesarean section delivery was more varied, ranging from 29% (95% CI (25%, 34%)) and going up to 56% (95% CI (53%, 59%)) (46,49,50,52). Dunne *et al* 2003, the only study to sample women with type 2 diabetes and exclude women with type 1 diabetes found 53% (95% CI (23%, 57%)) of pregnancies to women with type 2 diabetes were delivered via caesarean section (48). McAuliffe *et al* 1999 (46) found a lower prevalence of caesarean section delivery in comparison to the other studies that calculated estimates for women with type 1 diabetes separately. The study only included women that laboured spontaneously at or after 38 weeks gestation, these women are likely to have less complex pregnancies, better controlled diabetes, and less comorbidities than women that labour (spontaneously or induced) before 38 weeks gestation (Table 2.1, Figure 2.1).

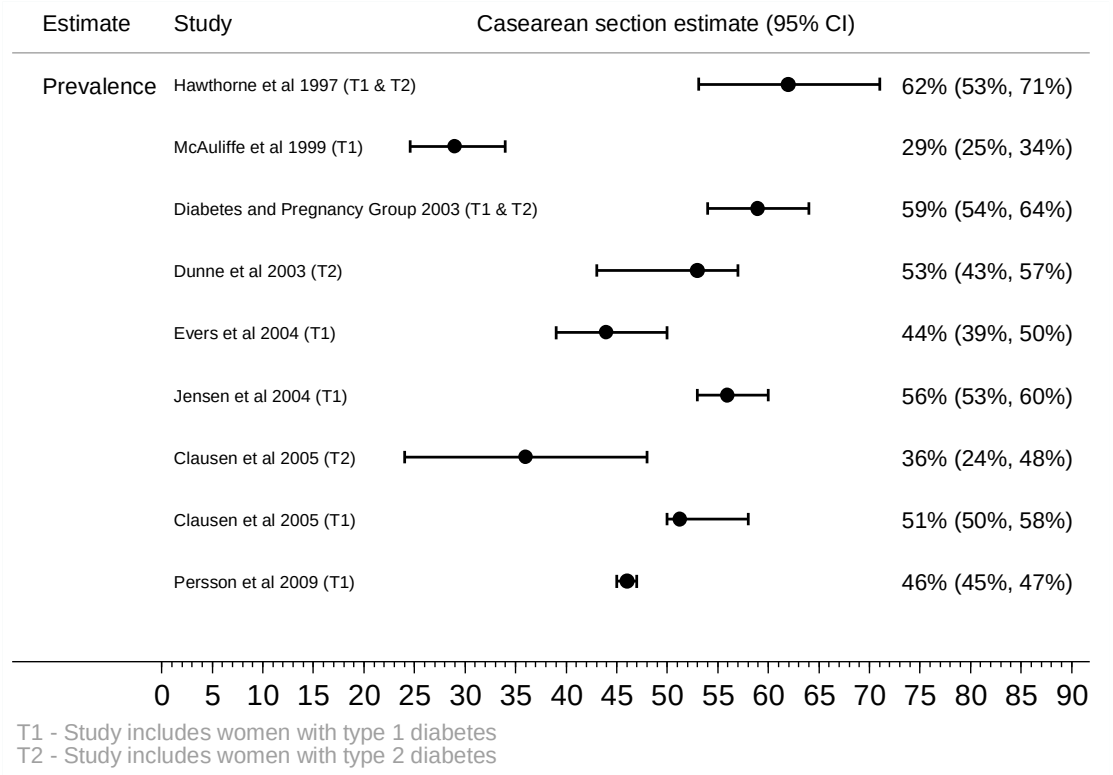
The relative risk for women with type 1 diabetes compared to the general population was very similar in Evers *et al* 2004 study in the Netherlands and Jensen *et al* 2004 study in Denmark. Evers and Jensen found women with type 1 diabetes had four times the risk of caesarean section when compared to the general population (49,50). Hawthorne *et al* 1997 found that the prevalence of caesarean section delivery was much higher in women with diabetes when compared to the background rate in the general population of the hospitals studied; the prevalence of caesarean section was 62% in women with diabetes compared to 10.4% - 17.5% among the background population (45). Clausen *et al* 2005 found there was weak evidence of a difference in the risk of caesarean section delivery

Table 2.1: Narrative literature review summary of studies examining caesarean section delivery in women with diabetes in pregnancy

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
Hawthorne *et al* 1997(45)	Prospective cohort UK	All hospitals caring for women with diabetes in pregnancy in Northern Britain. 111 pregnant women with insulin and non-insulin treated diabetes, resulting in 113 pregnancies	111 women	January to December 1994	Prevalence 62% (95% CI 53% to 71%)
McAuliffe *et al* 1999 (46)	Prospective cohort UK	A single clinic in Dublin, Ireland. Women with insulin dependent diabetes and no prior pregnancy complications were recruited at 38 weeks of gestation. Recruited 373 women	373 women	January 1981 to December 1994	Prevalence 29% (95% CI 25% to 34%)
Diabetes and pregnancy group 2003 (47)	Prospective survey France	All tertiary centres in France which cared for women with type 1 and type 2 diabetes were recruited. Recruited 435 singleton pregnancies, 289 to women with type 1 and 146 to women with type 2 diabetes	435 pregnancies	January 2000 to December 2001	Prevalence 59% (95% CI 54% to 64%)
Dunne *et al* 2003 (48)	Retrospective cohort UK	Maternity units in the West Midlands of Britain. 182 women with type 2 diabetes had pregnancies ending in the study period	182 pregnancies	1990 to 2002	Prevalence 53% (95% CI 43% to 64%)
Evers *et al* 2004 (49)	Prospective cohort Netherlands	All hospitals in the Netherlands. 323 women with type 1 diabetes presenting for antenatal care	353 women	April 1999 to April 2000	Prevalence 44% (95% CI 39% to 50%) Relative risk 3.7 (95% CI 3.2 to 4.2) compared to national data
Jensen *et al* 2004 (50)	Prospective cohort Denmark	All Danish hospitals. 1,218 women with type 1 diabetes recruited at 24 weeks gestation or termination at 24 weeks for ultra-sound verified severe	71,304 pregnancies	1993-1999	Prevalence 56% (95% CI 53%, 59%) Relative risk 4.4

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
		malformation comparison to background population			(95% CI 4.1 to 4.8) compared to national data
Clausen *et al* 2005 (51)	Retrospective cohort Denmark	Department of Obstetrics at a single hospital in Copenhagen. 61 women with pregestational type 2 diabetes were referred to the unit. For comparison 240 women with type 1 diabetes were selected from the same time period.	301 pregnancies	January 1996 to December 2001	Prevalence 36% (95% CI 24%, 48%) for women with type 2 diabetes Prevalence 51% (95% CI 50%, 58%) for women with type 1 diabetes Relative risk 1.42 (95% CI 0.99 to 2.03) comparing women with type 1 diabetes to women with type 2 diabetes
Persson *et al* 2009 (52)	Prospective cohort Sweden	All singleton births to women with type 1 diabetes in the Swedish birth registry and a control sample without type 1 diabetes were selected. 5,089 women with type 1 diabetes and 1,260,207 women without diabetes were recruited	1,265,296 pregnancies	1991-2003	Prevalence 46% (95% CI 45%, 47%) Adjusted OR 5.31 (95% CI 4.97 to 5.69) comparing women with type 1 diabetes to without diabetes

Figure 2.1: Forest plot of studies with an estimate of the prevalence of caesarean section delivery among women with diabetes in pregnancy



between women with type 1 and type 2 diabetes; relative risk 1.42 (95% CI (0.99, 2.03)) (51) (Table 2.1).

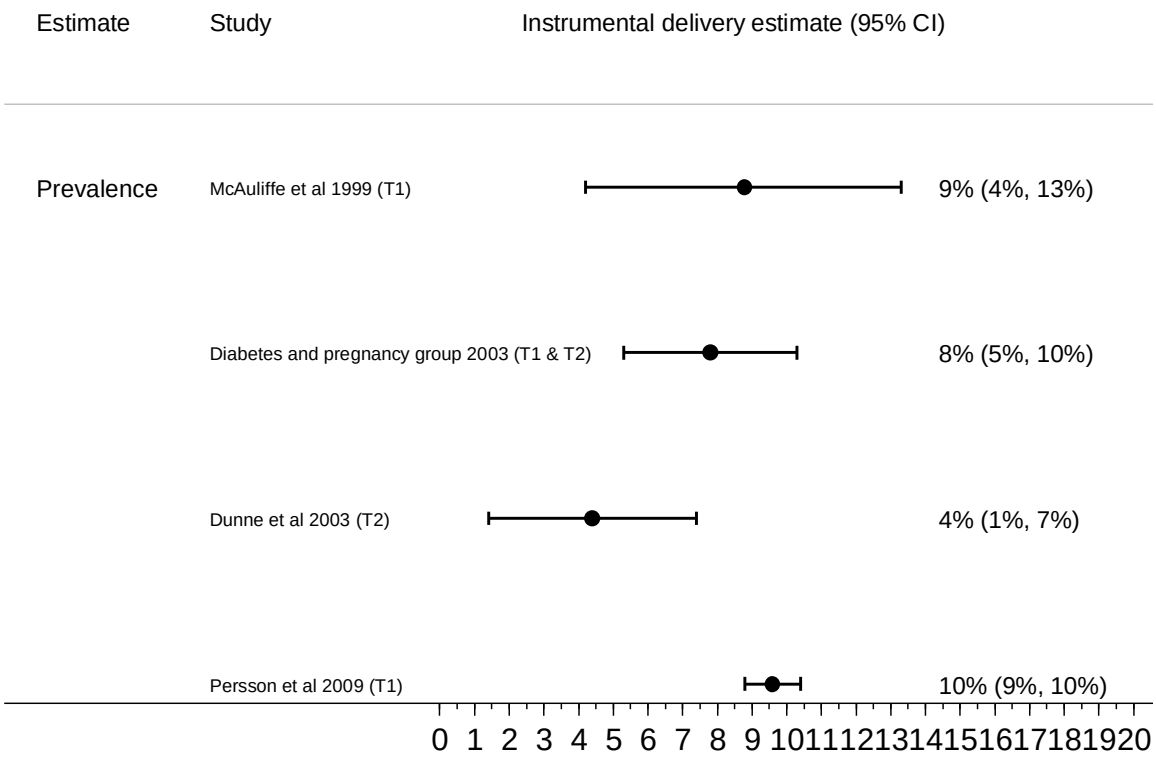
2.2.2 Instrumental delivery literature review

I found four studies with instrumental delivery as an outcome of interest among women with diabetes (46–48,52) (Table 2.2). All but one of the four studies recruited women from hospitals; one in Ireland (46), one in France (47), and the final one in the UK (West Midlands) (48). One of the studies selected women from a birth registry in Sweden (52). Two studies recruited women with type 1 diabetes; one with (52) and one without (46) a comparison population. Dunne et 2003 recruited women with type 2 diabetes, without a comparison group (48). The remaining study selected women with both type 1 and type 2 diabetes, without a control population (47). The McAuliffe *et al* 1999 study was a hospital based study that only selected women with type 1 diabetes from a single clinic in Dublin, Ireland. The study was fairly dated as the data was collected over two decades ago, between 1981 and 1994 (46). The Diabetes and Pregnancy Group 2003 recruited women with both type 1 and type 2 diabetes from tertiary care centres in France. Again,

Table 2.2: Narrative literature review summary of studies examining instrumental delivery in women with diabetes in pregnancy

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
McAuliffe *et al* 1999 (46)	Prospective cohort UK	A single clinic in Dublin, Ireland. Women with insulin dependent diabetes and no prior pregnancy complications were recruited at 38 weeks of gestation. Recruited 373 women	373 women	January 1981 to December 1994	Prevalence 7% (95% CI 4% to 9%)
Diabetes and pregnancy group 2003 (47)	Prospective survey France	All tertiary centres in France which cared for women with type 1 and type 2 diabetes were recruited. Recruited 435 singleton pregnancies, 289 to women with type 1 and 146 to women with type 2 diabetes	435 pregnancies	January 2000 to December 2001	Prevalence 8% (95% CI 5% to 10%)
Dunne *et al* 2003 (48)	Retrospective cohort UK	Maternity units in the West Midlands of Britain. 182 women with type 2 diabetes had pregnancies ending in the study period	182 pregnancies	1990 to 2002	Prevalence 4% (95% CI 1% to 7%)
Persson *et al* 2009 (52)	Prospective cohort Sweden	All singleton births to women with type 1 diabetes in the Swedish birth registry and a control sample without type 1 diabetes were selected. 5,089 women with type 1 diabetes and 1,260,207 women without diabetes were recruited	1,265,296 pregnancies	1991-2003	Prevalence 10% (95% CI 9%, 10%) Adjusted odds ratio 1.41 (95% CI 1.25 to 1.58) women with type 1 diabetes compared to women without

Figure 2.2: Forest plot of studies with an estimation of the prevalence of instrumental delivery among women with diabetes in pregnancy



the sample was quite dated and there was no control group (47). The Dunne *et al* 2003 study had a relatively small sample of 182 pregnancies to women with type 2 diabetes, selected from five maternity units within the West Midlands (48). The final study by Persson *et al* 2009 was considerably larger than the other three and had a control group, although they excluded women with type 2 diabetes (52).

The two studies that sampled women with type 1 diabetes both found that approximately 9% of women with type 1 diabetes experience an instrumental delivery. McAuliffe *et al* 1999 (46) and Persson *et al* 2009 reported that instrumental deliveries occurred in 9% (95% CI (4%, 13%)) and 10% (95% CI (9%, 10%)) of pregnancies to women with type 1, respectively. The French Diabetes and Pregnancy group 2003 (47) sampled women with both type 1 and type 2 diabetes and found a very similar prevalence of instrumental delivery of 8% (95% CI (5%, 10%)). Dunne *et al* 2003 found a slightly lower prevalence of deliveries among women with type 2 diabetes; 4% (95% CI (1%, 7%)) (48). Persson *et al* 2009 (52) also compared women with type 1 diabetes to the general pregnant population and found that women with type 1 diabetes had 41% higher odds of

instrumental delivery than women without diabetes in pregnancy; OR 1.41 (95% CI (1.25, 1.58)) (Table 2.2, Figure 2.2).

2.2.3 Pregnancy induced hypertension, preeclampsia, and eclampsia literature review

There were six studies with pregnancy induced hypertension (PIH), preeclampsia or eclampsia as an outcome of interest among pregnant women with diabetes (47–52) (Table 2.3). Five of the six studies selected women from hospital clinics (47–51), and the sixth used a national birth registry (52). Three studies selected women with type 1 diabetes and excluded women with the type 2 diabetes (49,50,52), one study selected women with type 2 diabetes and excluded women with type 1 diabetes (48), and the final two studies selected women with both type 1 and type 2 diabetes (47,51). Three out of the six studies had a comparison population; one study selected women with type 1 diabetes and a control population (52) and the other two studies compared women with type 1 diabetes to women with type 2 diabetes (47,51).

The prevalence of preeclampsia ranged from 10% (95% CI (9%, 11%)) to 18% (95% CI (16%, 20%)) in the studies with women with type 1 diabetes (49,50,52). The Diabetes and pregnancy group 2003 and Clausen *et al* 2005 found that among women with type 1 and type 2 diabetes the prevalence of preeclampsia was very similar (47,51). For women with type 1 diabetes they found the prevalence of preeclampsia to be: 19% (95% CI (14%, 23%)) and 13% (95% CI (8%, 17%)), and for women with type 2 diabetes they found the prevalence of preeclampsia to be: 18% (95% CI (12%, 24%)) and 7% (95% CI (1%, 13%)), respectively (47,51). Whereas, Dunne *et al* 2003 found that the prevalence of preeclampsia was marginally higher among women with type 2 diabetes: 20% (95% CI (14%, 26%)) (48) (Table 2.3, Figure 2.2).

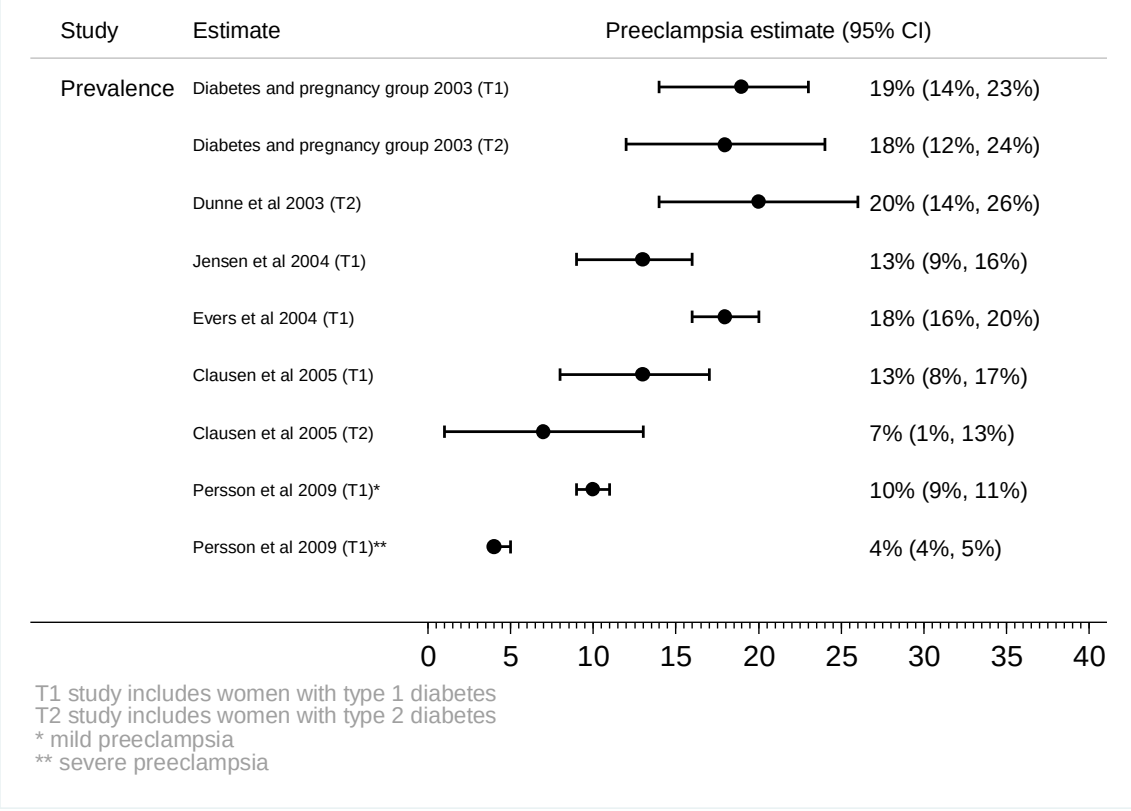
Evers *et al* 2004, found that women with type 1 diabetes have 12 times the risk of preeclampsia when compared to the general population; relative risk 12.1 (95% CI (9.0, 16.1)) (49). Persson *et al* 2009 found that women with type 1 diabetes had over four times the odds of experiencing mild and severe preeclampsia when compared to women without diabetes in pregnancy (52). Clausen *et al* 2005 found that the risk of preeclampsia was no different for women with type 1 diabetes compared to women with type 2 diabetes: relative risk 1.07 (95% CI (0.57, 2.00)) (51) (Table 2.3).

Table 2.3: Narrative literature review summary of studies examining preeclampsia in women with diabetes in pregnancy

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
Diabetes and pregnancy group 2003 (47)	Prospective survey France	All tertiary centres in France which cared for women with type 1 and type 2 diabetes were recruited. Recruited 435 singleton pregnancies, 289 to women with type 1 and 146 to women with type 2 diabetes	435 pregnancies	January 2000 to December 2001	Prevalence 19% (95% CI 14% to 23%) for women with type 1 diabetes Prevalence 18% (95% CI 12% to 24%) for women with type 2 diabetes
Dunne *et al* 2003 (48)	Retrospective cohort UK	Maternity units in the West Midlands of Britain. 182 women with type 2 diabetes had pregnancies ending in the study period	182 pregnancies	1990 to 2002	Prevalence 20% (95% CI 14% to 26%)
Evers *et al* 2004 (49)	Prospective cohort Netherlands	All hospitals in the Netherlands/323 women with type 1 diabetes presenting for antenatal care	323 women	April 1999 to April 2000	Prevalence 13% (95% CI 9% to 16%) Relative risk 12.1 (95% CI 9.0 to 16.1) women with type 1 diabetes compared to general population
Jensen *et al* 2004 (50)	Prospective cohort Denmark	All Danish hospitals. 1,218 women with type 1 diabetes recruited at 24 weeks gestation or termination at 24 weeks for ultra-sound verified severe malformation comparison to background population	71,304 pregnancies	1993-1999	Prevalence 18% (95% CI 16% to 20%)
Clausen *et al* 2005 (51)	Retrospective cohort Denmark	Department of Obstetrics at a single hospital in Copenhagen. 61 women with pregestational type 2 diabetes were referred to the unit. For	301 pregnancies	January 1996 to December 2001	Prevalence 13% (95% CI 8% to 17%) for women with type 1 diabetes

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
		comparison 240 women with type 1 diabetes were selected from the same time period.			Prevalence 7% (95% CI 1% to 13%) for women with type 2 diabetes Relative risk 1.07 (95% CI 0.57 to 2.00) women with type 1 diabetes compared to women with type 2 diabetes
Persson *et al* 2009 (52)	Prospective cohort Sweden	All singleton births to women with type 1 diabetes in the Swedish birth registry and a control sample without type 1 diabetes were selected. 5,089 women with type 1 diabetes and 1,260,207 women without diabetes were recruited	1,265,296 pregnancies	1991-2003	Prevalence 10% (95% CI 9% to 11%) for mild preeclampsia Prevalence 4% (95% CI 4% to 5%) for severe preeclampsia Adjusted odds ratio comparing women with type 1 diabetes to women without diabetes mild 4.30 (95% CI 3.83 to 4.83) severe 5.31 (95% CI 4.97 to 5.69)

Figure 2.3: Forest plot of studies with an estimate of the prevalence of pregnancy induced hypertension, preeclampsia or eclampsia among women with diabetes in pregnancy



2.2.4 Perinatal mortality literature review

There were 14 studies that included perinatal mortality among women with diabetes as an outcome of interest (34,43,45–48,50,52–55) (Table 2.4). All but one study (52) selected women with diabetes from hospital clinics. One study selected only women with type 2 diabetes and excluded women with type 1 diabetes (48), seven studies selected only women with type 1 diabetes (43,46,49,50,52,53,55), and six studies selected women with both type 1 and type 2 diabetes (34,43,45,47,54,56). Two studies compared the general population to women with type 1 (50,52), two studies compared women with type 1 and type 2 diabetes to the general population (34,45,56), and one study compared women with type 1 diabetes to women with type 2 diabetes (51). Dunne *et al* 2003 were the only study to just sample women with type 2 diabetes and found a perinatal mortality prevalence of 24.6 (95% CI (0.8, 48.4)) per 1,000 births (48). The perinatal mortality prevalence found in the seven studies that just sampled women with type 1 diabetes ranged from 20.0 (95% CI (16.2, 23.8)) per 1,000 births to 50.9 (95% CI (28.6, 73.3)) per 1,000 births (43,46,49,50,52,53,55) (Table 2.4, Figure 2.4).

Six studies examined both type 1 and type 2 diabetes, three presented combined estimates. Hawthorne *et al* 1999, Macintosh *et al* 2006, and Bell *et al* 2008 found the prevalence of perinatal mortality for women with type 1 and type 2 diabetes was 48.0 (95% CI 6.9, 88.4)) per 1,000 pregnancies, 43.0 (95% CI (30.4, 55.6)) per 1,000 pregnancies, and 31.7 (95% CI (21.2, 42.2)) per 1,000 pregnancies, respectively (34,45,56). Cundy *et al* 2000 found a much lower prevalence of perinatal mortality in women with type 1 diabetes 12.5 (95% CI (1.5, 44.4)) per 1,000 births when compared to the other literature. But, the prevalence of perinatal mortality found among women with type 2 diabetes in the same study was similar to the other literature: 46.1 (95% CI (28.6, 73.3)) per 1,000 births (Table 2.4, Figure 2.4).

Hawthorne *et al* 1997 found that women with pregestational diabetes had over five times the odds of perinatal mortality compared to the general pregnant population, OR 5.38 (95% CI (2.27, 12.70)) (45). Macintosh *et al* 2006 found an age adjusted relative risk of nearly four, comparing women with pregestational diabetes to the general population: age adjusted relative risk 3.8 (95% CI (3.0, 4.7)) per 1,000 pregnancies.

The French Diabetes and Pregnancy Group 2003 and Clausen *et al* 2005 both found that there is no difference in the risk of perinatal mortality between women with type 1 and type 2 diabetes (47,51). Evers *et al* 2004 and Jensen *et al* 2004 found that women with type 1 diabetes had approximately four times the risk of perinatal mortality compared to the general population (49,50). Persson *et al* 2009 found that women with type 1 diabetes had just over three times the odds of perinatal mortality when compared to women without diabetes: adjusted odds ratio 3.29 (95% CI (2.50, 4.33)) (52) (Table 2.4).

Table 2.4: Narrative literature review summary of studies examining perinatal death in women with diabetes in pregnancy

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
Hawthorne *et al* 1997 (45)	Prospective cohort UK	All hospitals caring for women with diabetes in pregnancy in Northern Britain/111 pregnant women with insulin and non-insulin treated diabetes, resulting in 113 pregnancies	113 pregnancies	January to December of 1994	Prevalence 48.0 (95% CI 6.9 to 88.4) per 1,000 Odds ratio 5.38 (95% CI 2.27 to 12.70) compared to general population
Casson *et al* 1997 (53)	Cohort UK	Maternity units in the north west of England caring for women with insulin dependent diabetes. 462 pregnancies in 355 women over the study period	462 pregnancies	1990-1994	Prevalence 36.1 (95 % CI 16.8 to 55.4) per 1,000 total births
McAuliffe *et al* 1999 (46)	Prospective cohort UK	A single clinic in Dublin, Ireland. Women with insulin dependent diabetes and no prior pregnancy complications were recruited at 38 weeks of gestation. Recruited 373 women	373 women	January 1981 to December 1994	Prevalence 50.9 (95% CI 28.6 to 73.3) per 1,000 pregnancies
Cundy *et al* 2000 (54)	Cohort New Zealand	Women attending the National Women's hospital in Auckland during the study period with known or gestational diabetes were recruited. 1,526 infants born to women with diabetes, 160 (10%) were affected by type 1 diabetes, 256 (17%) affected by type 2 diabetes and the remaining 1,110 (73%) affected by gestational diabetes.	83,551 pregnancies	1st July 1985 to 30 June 1997	Prevalence 12.5 (95% CI 1.5 to 44.4) per 1,000 for women with type 1 diabetes Prevalence 46.1 (95% CI 26.4 to 65.8) per 1,000 for women with type 2 diabetes*
Platt *et al* 2002 (43)	Retrospective cohort	All women with type 1 diabetes attending one of 10 maternity units in	547 pregnancies	1995-1999	Prevalence 43.0 (95% CI 26.5 to 65.6) per 1,000 total births

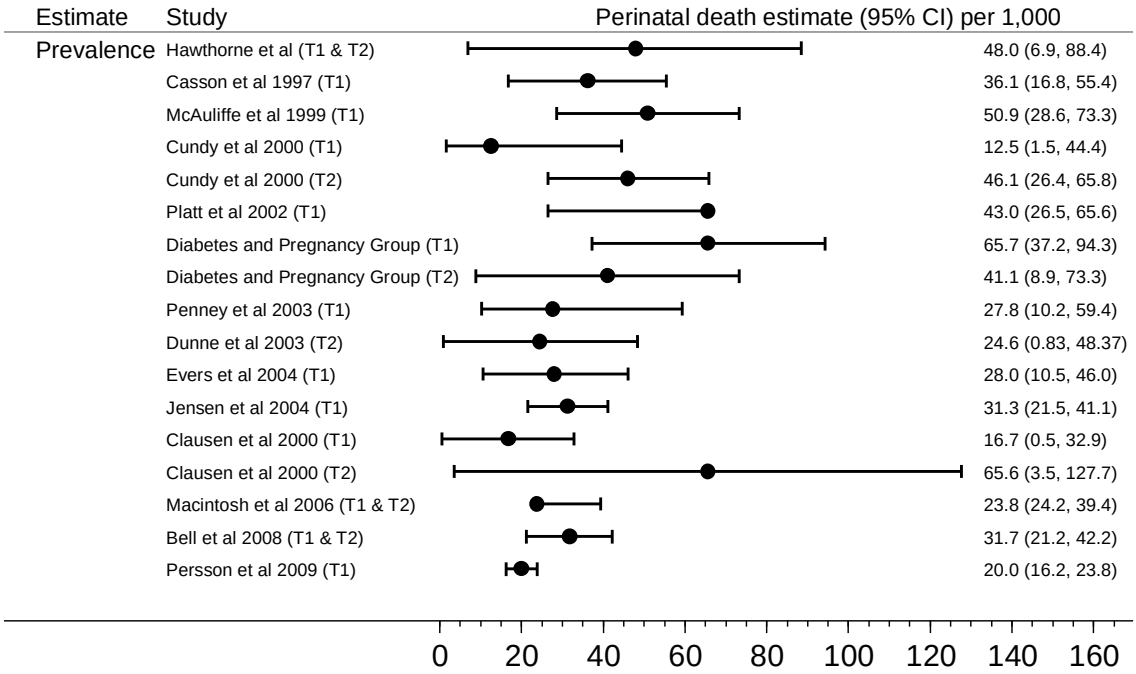
Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
	UK	North-West of England. 547 pregnancies were recruited			
Diabetes and pregnancy group 2003 (47)	Prospective survey France	All tertiary centres in France which cared for women with type 1 and type 2 diabetes were recruited. Recruited 435 singleton pregnancies, 289 to women with type 1 and 146 to women with type 2 diabetes	435 pregnancies	January 2000 to December 2001	Prevalence 65.7 (95% CI 37.2 to 94.3) per 1,000 for women with type 1 diabetes Prevalence 41.1 (95% CI 8.9 to 73.3) per1,000 for women with type 2 diabetes Relative risk 1.60 (95% CI 0.65 to 3.92) for women with type 1 diabetes compared to women with type 2 diabetes
Penney *et al* 2003 (55)	Prospective cohort UK	All women with type 1 diabetes prior to pregnancy attending one of 22 maternity units in Scotland were recruited. Sample size was 216 babies	216 babies	1st April 1998 to 31st March 1999	Prevalence 27.8 (95% CI 10.2 to 59.4) per 1,000 total births
Dunne *et al* 2003 (48)	Retrospective cohort UK	Maternity units in the West Midlands of Britain. 182 women with type 2 diabetes had pregnancies ending in the study period	182 pregnancies	1990 to 2002	Prevalence 24.6 (95% CI 0.83, 48.37) per 1,000
Evers *et al* 2004 (49)	Prospective cohort Netherlands	All hospitals in the Netherlands/323 women with type 1 diabetes presenting for antenatal care	323 pregnancies	April 1999 to April 2000	Prevalence 28.0 (95% CI 10.5 to 46.0) per 1,000 Relative risk 3.5

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
					(95% CI 1.8 to 6.7) type 1 compared to general population
Jensen *et al* 2004 (57)	Prospective cohort Denmark	All Danish hospitals. 1,218 women with type 1 diabetes recruited at 24 weeks gestation or termination at 24 weeks for ultra-sound verified severe malformation comparison to background population	71,304 pregnancies	1993-1999	Prevalence 31.3 (95% CI 21.5 to 41.1) per 1,000 Risk ratio 4.1 (95% CI 2.9 to 5.6) compared to general population
Clausen *et al* 2005 (51)	Retrospective cohort Denmark	Department of Obstetrics at a single hospital in Copenhagen. 61 women with pregestational type 2 diabetes were referred to the unit. For comparison 240 women with type 1 diabetes were selected from the same time period.	301 pregnancies	January 1996 to December 2001	Prevalence 65.6 (95% CI 3.5 to 127.7) per 1,000 for women with type 2 diabetes Prevalence 16.7 (95% CI 0.5 to 32.9) per 1,000 for women with type 1 diabetes Relative risk 4.0 (95% CI 1.0 to 15.5) women with type 1 diabetes compared to women with type 2 diabetes
Macintosh *et al* 2006 (56)	Cohort UK	All women with type 1 and type 2 diabetes delivering at a maternity units in England, Wales and Northern Ireland were recruited. Sample size was 2,359 pregnancies, 27.6% to women with type 2 diabetes.	2,359 pregnancies	March 2002 to February 2003	Prevalence 23.8 (95% CI 24.2 to 39.4) per 1,000 for women with diabetes

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
					Age adjusted relative risk 3.8 (95% CI 3.0 to 4.7) per 1,000 pregnancies women with diabetes compared to national data
Bell *et al* 2008 (34)	Longitudinal survey UK	Northern Diabetic Pregnancy Survey (NorDiP) collected information on all women with pregestational diabetes delivering in one of 14 consultant led units in the North of England data is linked to congenital malformation and perinatal mortality databases. Sample size was 1,258 pregnancies, resulting in 1,279 offspring, 15% were women with type 2 diabetes.	1,258 pregnancies	January 1996 to December 2004	Prevalence 31.7 (95% CI 21.2 to 42.2) per 1,000 births for women with diabetes
Persson *et al* 2009 (52)	Prospective cohort Sweden	All singleton births to women with type 1 diabetes in the Swedish birth registry and a control sample without type 1 diabetes were selected. 5,089 women with type 1 diabetes and 1,260,207 women without diabetes were recruited	1,265,296 pregnancies	1991-2003	Prevalence 20.0 (95% CI 16.2 to 23.8) per1,000 for women with type 1 diabetes Adjusted odds ratio 3.29 (95% CI 2.50 to 4.33) comparing women with type 1 and without diabetes

* This estimate is for women with type 2 diabetes that was diagnosed prior to pregnancy and during pregnancy

Figure 2.4: Forest plot of studies with an estimate of the prevalence of perinatal death among women with diabetes in pregnancy



T1 study includes women with type 1 diabetes
T2 study includes women with type 2 diabetes

2.2.5 Congenital malformations literature review

Thirteen studies examined congenital malformations among women with diabetes in pregnancy (Table 2.5) (34,43,45,47–53,55,56,58). Again, all but one of the studies selected women with diabetes from a hospital setting (52). Six studies selected women with type 1 diabetes and excluded women with type 2 diabetes (43,49,52,53,55,57), one study selected women with type 2 diabetes and excluded women with type 1 diabetes (48), and six studies selected women with type 1 and type 2 diabetes (34,45,47,51,56,58).

The prevalence of congenital malformations among women with type 1 diabetes in pregnancy ranged from 47.0 (95% CI (45.6, 48.4)) per 1,000 births to 94.0 (95% CI (65.9, 120.1)) per 1,000 pregnancies (43,49,52,53,55,57). Dunne *et al* 2003, the only study to sample just women with type 2 diabetes, found a prevalence of major congenital malformation of 98.9 (95% CI (55.5, 80.7)) per 1,000 pregnancies (48). Six studies sampled women with both type 1 and type 2 diabetes and four presented separate prevalence estimates which ranged from 29.0 (95% CI (7.9, 50.5)) per 1,000 pregnancies to 82.2 (95% CI (67.9, 98.3)) per 1,000 pregnancies for women with type 1 diabetes and

from 34.2 (95% CI (4.7, 63.7)) per 1,000 pregnancies to 65.6 (95% CI (3.5, 127.7)) per 1,000 pregnancies for women with type 2 diabetes (47,51,56,58). The combined prevalence estimates of major congenital malformations for women with type 1 and type 2 diabetes ranged from 75.0 (95% CI (55.5 86.3)) per 1,000 pregnancies to 82.6 (95% CI (30.9, 134.2)) per 1,000 pregnancies (34,45) (Table 2.5, Figure 2.5).

Clausen *et al* 2005 and Bell *et al* 2012 found that there was no difference in the risk of major congenital malformations experienced by women with type 1 and type 2 diabetes (51,58). Three studies compared the risk of major congenital malformations between women with type 1 and type 2 diabetes and the general pregnant population (45,56,58). Macintosh *et al* 2006 reported a prevalence ratio of 2.2 (95% CI (1.8, 2.6)) comparing women with pregestational diabetes to the EUROCAT data (56). Hawthorne *et al* 1997 and Bell *et al* 2012 found women with pregestational diabetes had over three times the risk of major congenital malformations when compared to the general population (45,58) (Table 2.5).

The three remaining studies compared the risk of major congenital malformations among women with type 1 diabetes to the general pregnant population. Evers *et al* 2004 found that women with type 1 diabetes in pregnancy had over three times the risk of congenital malformations when compared to the general population, relative risk 3.4 (95% CI (2.4, 4.8)) (49). Whereas, Jensen *et al* 2004 found that women with type 1 diabetes only had a 70% increased risk of congenital malformations when compared to the general population, relative risk 1.7 (95% CI (1.3, 2.2)) (50). Persson *et al* 2009 found that pregnant women with type 1 diabetes had nearly three times the odds of experiencing a major congenital malformations when compared to the general pregnancy population; odds ratio 2.50 (95% CI (2.13, 2.94)) (52) (Table 2.5).

Table 2.5: Narrative literature review summary of studies examining major congenital malformations in women with diabetes in pregnancy

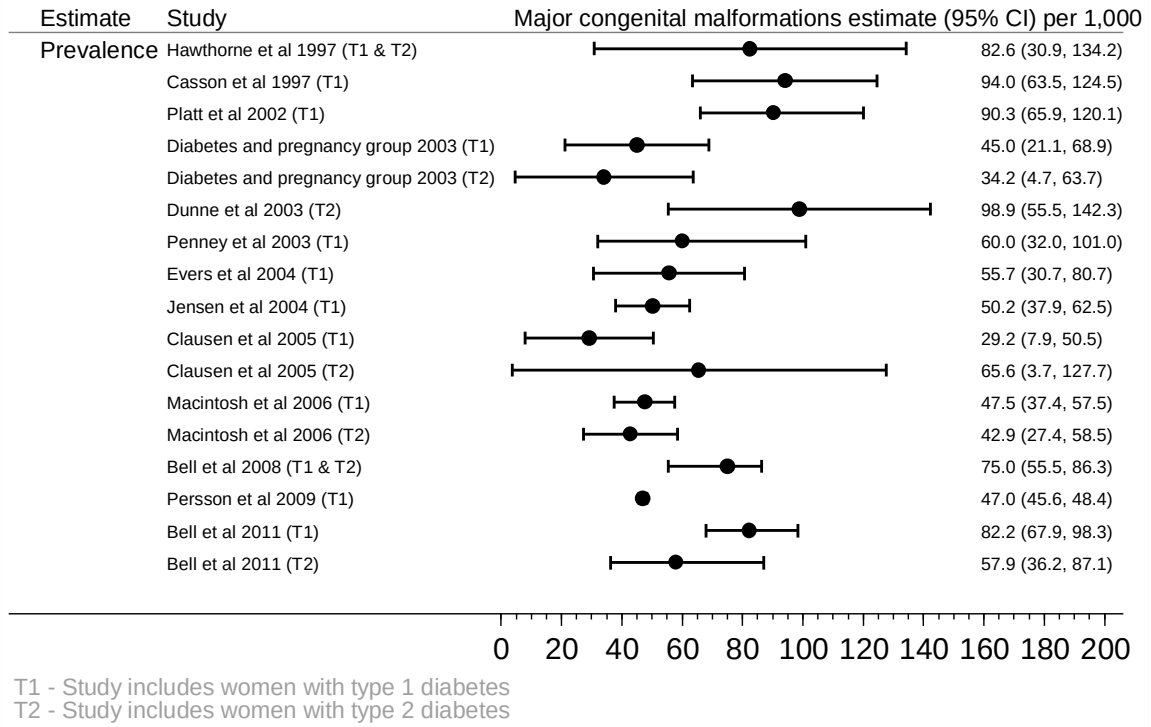
Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
Hawthorne *et al* 1997 (45)	Prospective cohort UK	All hospitals caring for women with diabetes in pregnancy in Northern Britain. 111 pregnant women with insulin and non-insulin treated diabetes, resulting in 113 pregnancies	113 pregnancies	January to December of 1994	Prevalence 82.6 (95% CI 30.9 to 134.2) per 1,000 Relative risk 3.76 (95% CI 2.00 to 7.06) compared to regional rate
Casson *et al* 1997 (53)	Cohort UK	Maternity units in the north west of England caring for women with insulin dependent diabetes. 462 pregnancies in 355 women over the study period	462 pregnancies	1990-1994	Prevalence 94.0 (95 % CI 63.5 to 124.5) per 1,000 total births
Platt *et al* 2002 (43)	Retrospective cohort UK	All women with type 1 diabetes attending one of 10 maternity units in North-West of England. 547 pregnancies were recruited	547 pregnancies	1995-1999	Prevalence 90.3 (95% CI 65.9 to 120.1) per 1,000 total births
Diabetes and pregnancy group 2003 (47)	Prospective survey France	All tertiary centres in France which cared for women with type 1 and type 2 diabetes were recruited. Recruited 435 singleton pregnancies, 289 to women with type 1 and 146 to women with type 2 diabetes	435 pregnancies	January 2000 to December 2001	Prevalence 45.0 (95% CI 21.1 to 68.9) per 1,000 in women with type 1 diabetes Prevalence 34.2 (95% CI 4.7 to 63.7) per 1,000 in women with type 2 diabetes
Dunne *et al* 2003 (48)	Retrospective cohort UK	Maternity units in the West Midlands of Britain. 182 women with type 2 diabetes had pregnancies ending in the study period	182 pregnancies	1990 to 2002	Prevalence 98.9 (95% CI 55.5 to 142.3) per 1,000
Penney *et al* 2003 (55)	Prospective cohort	All women with type 1 diabetes prior to pregnancy attending one of 22	216 pregnancies	1st April 1998 to 31st March 1999	Prevalence 60 (95% CI 32 to 101) per 1,000 total births

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
	UK	maternity units in Scotland were recruited. Sample size was 216 babies			
Evers *et al* 2004 (49)	Prospective cohort Netherlands	All hospitals in the Netherlands/323 women with type 1 diabetes presenting for antenatal care	323 pregnancies	April 1999 to April 2000	Prevalence 55.7 (95% CI 30.7 to 80.7) per 1,000 for women with type 1 diabetes Relative risk 3.4 (95% CI 2.4 to 4.8) for women with type 1 diabetes compared to the general population
Jensen *et al* 2004 (50)	Prospective cohort Denmark	All Danish hospitals. 1218 women with type 1 diabetes recruited at 24 weeks gestation or termination at 24 weeks for ultra-sound verified severe malformation comparison to background population	71,304 pregnancies	1993-1999	Prevalence 50.2 (95% CI 37.9 to 62.5) per 1,000 for women with type 1 diabetes Relative risk 1.7 (95% CI 1.3 to 2.2) for women with type 1 diabetes compared to the general population
Clausen *et al* 2005 (51)	Retrospective cohort Denmark	Department of Obstetrics at a single hospital in Copenhagen. 61 women with pregestational type 2 diabetes were referred to the unit. For comparison 240 women with type 1 diabetes were selected from the same time period	301 pregnancies	January 1996 to December 2001	Prevalence 29.0 (95% CI 7.9 to 50.5) per 1,000 for women with type 1 diabetes Prevalence 65.6 (95% CI 3.5 to 127.7) per 1,000 for women with type 2 diabetes Relative risk 2.3 (95% CI 0.7 to 1.47) women with type 1 diabetes compared to women with type 2 diabetes

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
Macintosh *et al* 2006 (56)	Cohort UK	All women with type 1 and type 2 diabetes delivering at maternity units in England, Wales and Northern Ireland were recruited. Sample size was 2359 pregnancies, 27.6% to women with type 2 diabetes.	2,359 pregnancies	March 2002 to February 2003	Prevalence 47.5 (95% CI 37.4 to 57.5) per 1,000 for women with type 1 diabetes Prevalence 42.9 (95% CI 27.4 to 58.5) per 1,000 for women with type 2 diabetes Prevalence ratio 2.2 (95% CI 1.8 to 2.6) women with diabetes compared to data from EUROCAT
Bell *et al* 2008 (34)	Longitudinal survey UK	Northern Diabetic Pregnancy Survey (NorDiP) collected information on all women with pregestational diabetes delivering in one of 14 consultant led units in the North of England data is linked to congenital malformation and perinatal mortality databases/ Sample size was 1258 pregnancies, resulting in 1279 offspring, 15% were women with type 2 diabetes.	1,258 pregnancies	January 1996 to December 2004	Prevalence 75 (95% CI 55.5 to 86.3) per 1,000 births for women with diabetes
Persson *et al* 2009 (52)	Prospective cohort Sweden	All singleton births to women with type 1 diabetes in the Swedish birth registry and a control sample without type 1 diabetes were selected. 5,089 women with type 1 diabetes and 1,260,207 women without diabetes were recruited	1,265,296 pregnancies	1991-2003	Prevalence 47.0 (95% CI 45.6 to 48.4) per 1,000 for women with type 1 diabetes Odds ratio 2.50 (95 % CI 2.13 to 2.94) for women with type 1 diabetes compared to the general population
Bell *et al* 2012 (58)	Longitudinal survey UK	All women delivering singleton pregnancies (live, still, late foetal loss and terminations) in the study region. Women with pregestational diabetes	401,149 pregnancies	January 1996 to December 2008	Prevalence 82.2 (95% CI 67.9 to 98.3) per 1,000 for women with type 1 diabetes

Author and Year	Design and Country	Setting and Study population	Sample size	Study period	Results
		were identified from NorDiP. Sample size was 401,149 pregnancies, 0.42% were women with pregestational diabetes, type 2 diabetes affected 21.6% of pregnancies with diabetes.			Prevalence 57.9 (95% CI 36.2 to 87.1) per 1,000 for women with type 2 diabetes Relative risk 1.4 (95% CI 0.9 to 2.2) for women with diabetes compared to the general population

Figure 2.5: Forest plot of studies with an estimate of the prevalence of major congenital malformations among women with diabetes in pregnancy



2.3 Discussion of narrative literature review

2.3.1 General findings

There are 15 studies presented here; the majority of the studies investigated more than one adverse pregnancy outcome. The most commonly examined outcome was major congenital malformations, which was examined in 14 out of the 15 studies reviewed. Below I discuss the strengths and weaknesses of each of the studies.

2.3.2 Strengths and weaknesses

2.3.2.1 Size

The largest study was conducted in Sweden, using birth registry data with over five thousand pregnant women with type 1 diabetes identified from electronic health records (52). Even in the smallest study over one hundred women with type 1 diabetes were recruited. With a smaller sample size there was the potential for reduced power to detect a difference between women with and without diabetes in pregnancy for rarer outcomes, such as perinatal death or major congenital malformations. Although the paper by

Hawthorne *et al* did find a significantly increased risk of both perinatal death and major congenital malformations for women with type 1 diabetes compared to the general population (45).

2.3.2.2 Setting

In all but one of the studies women with diabetes in pregnancy were identified in hospitals or maternity units. The only population based study, by Persson *et al* 2009, identified pregnant women with diabetes via the Swedish Medical Birth Registry, which contains >98% of all deliveries that occur in Sweden (59). Women that deliver in a hospital or maternity unit may be at a higher risk or believed to be at a higher risk of experiencing adverse pregnancy outcomes, such as caesarean section, compared to women that do not deliver in a hospital. Also, women that deliver in a maternity unit are likely to be considered to have lower risk pregnancy than women that deliver in a hospital. Therefore, hospital and maternity based samples are potentially not representative of the population.

2.3.2.3 Diabetes type

The pregnant woman's type of diabetes was mostly ascertained prospectively; when the mother attended a hospital clinic at booking or delivery of the pregnancy. Some studies also used midwife and other medical notes. The full medical history for each woman was unlikely to be known and may have led to inaccuracies in the classification of diabetes type. Such as when obsolete terminology was used, for example: insulin dependent diabetes. Some of these women may have had type 2 diabetes but were treated with insulin and as their full medical records were not known they were misclassified as insulin dependent diabetics.

Nine out of the 15 studies excluded women with type 2 diabetes, one excluded women with type 1 diabetes and the remaining five studies selected women with both type 1 and type 2 diabetes. Type 2 diabetes may have been considered a less severe type of diabetes, with women affected by type 2 diabetes during pregnancy expected to have a lower risk of adverse pregnancy outcomes in comparison to type 1 diabetes. This could explain why women with type 2 diabetes were frequently excluded when pregestational diabetes was examined in the literature. From this review we can see that women with type 2 diabetes have similar risk of adverse pregnancy outcomes as women with type 1 diabetes in pregnancy. Clausen *et al* 2005 found that there was no difference in the risk

of caesarean section, preeclampsia, perinatal death or major congenital malformations between women with type 1 and type 2 diabetes (51).

2.3.2.4 Comparison population

Half of the studies presented did not have a comparison population (34,43,46,49,53–55). Five studies compared the prevalence of adverse pregnancy outcomes found in women with pregestational diabetes to national or regional rates and all studies found women with diabetes in pregnancy had higher rates of adverse outcomes (45,47,48,50,56). Macintosh *et al* 2006 and Clausen *et al* 2005 (51,56) also compared the rates of adverse pregnancy outcomes between women with type 1 and type 2 diabetes. Four other studies selected women with type 1 or type 2 diabetes but did not present prevalence estimates for these groups separately.

2.3.3 Summary

Women with pregestational diabetes in pregnancy are at a higher risk of experiencing: caesarean section delivery, instrumental delivery, preeclampsia, perinatal death, and major congenital malformations. But with such varied study designs and comparison groups it is difficult to clarify whether there has been any change over time in the rate of adverse pregnancy outcomes for women with type 1 and type 2 diabetes since the St Vincent declaration.

In the next chapter I introduce the main research questions of the thesis alongside a complete overview of the thesis.

Chapter 3 Aims and Objectives

3.1 Introduction

In the previous chapter I presented the findings from my review of the current literature. In this chapter I introduce my research questions and provide a complete overview of the thesis. This chapter will end with the main aims and objectives of the thesis.

The overall aim and research question of this thesis was to assess whether women with type 1 and type 2 diabetes are at an increased risk of adverse pregnancy outcomes when compared to women without diabetes using a large primary care database. The hypothesis I am testing is that women with pregestational diabetes in pregnancy remain at an increased risk of adverse pregnancy outcomes in comparison to women without diabetes in pregnancy. The thesis has three results chapters which present the study design, methodologies, and findings from each study, that combine to answer the overall research question. The first two results chapters (Chapter 6 and Chapter 7) are the two background studies that focus on validating the recording of the exposure (pregestational diabetes) and the five outcomes of interest (caesarean section, instrumental delivery, preeclampsia, perinatal death, and major congenital malformations) in the primary care database. The third and final results chapter (Chapter 8) is the cohort study, which aims to address the main research question.

Each of the three PhD studies utilise a primary care database; The Health Improvement Network (THIN). I describe THIN in detail in the next chapter. As well as having an overall aim, each of the three PhD studies have a number of objectives and these are outlined below.

3.1.1 Study one – Pregestational type 1 and type 2 diabetes in pregnancy

The overall aim of the first study of the PhD was to investigate pregestational diabetes in pregnancy using the primary care database. The study specific objectives are:

1. To compare socio-demographic and other characteristics between pregnant women with and without pregestational diabetes mellitus.
2. Investigate temporal trends in the prevalence of pregestational diabetes mellitus affecting pregnancy between January 1995 and December 2012.

3. Explore which antidiabetic therapies are prescribed to women with pregestational diabetes mellitus during pregnancy.

3.1.2 Study two – Prevalence of adverse maternal and child pregnancy outcomes in the general population in primary care

The overall aims of this study are to investigate the validity of the recording of the selected adverse outcomes in THIN compared with the UK population. The study specific objectives are:

1. Calculate the prevalence of each outcome in the pregnancy cohort.
2. Examine the temporal changes in the prevalence of each outcome over the study period.
3. Examine the associations between maternal demographic and clinical characteristics with each outcome.

3.1.3 Study three - The risk of adverse maternal and child pregnancy outcomes due to pregestational diabetes in pregnancy

This study is where the overall aim of the thesis is addressed; assessing whether women with type 1 and type 2 diabetes in pregnancy are at an increased risk of adverse pregnancy outcomes. The study specific objectives are:

1. Calculate the absolute risk and risk difference of each of the outcomes for women with type 1, type 2 diabetes, and without diabetes.
2. Calculate temporal trends in the absolute risk of each of the outcomes adjusting for differences in maternal characteristics in women with and without diabetes.
3. Calculate the risk ratio of each of the outcomes adjusting for differences in maternal characteristics in women with and without diabetes.

3.2 Summary

In this chapter I have introduced the main aim and research questions of the thesis and presented the specific research objectives for each of the three studies included. In the next chapter I will introduce primary care within the United Kingdom and will describe the

primary care database that is used for each of three studies in the thesis, including the main strengths and limitations of the database.

Chapter 4 Primary Care and The Health Improvement Network database

4.1 Primary Care

4.1.1 The National Health Service in the United Kingdom

The National Health Service (NHS) was launched in the United Kingdom (UK) in 1948, with the key aim and ideal of providing good quality health care to all residents of the UK regardless of wealth. The NHS still provides services to residents that are free at the point of access, with the exception of some charges for prescriptions, optical, and dental care. All legal residents of the UK can access health care without charge at the point of contact.

The NHS consists of primary care providers and secondary care providers. Primary care includes general practitioners (GPs), NHS walk-in or drop in centres, community pharmacists, dentists, and optometrists; they are the local or community based services that any resident of the UK can access. Primary care professionals are often referred to as the 'gate keepers' of the NHS as they will be the first point of contact for most patients and will decide whether a patient needs to be referred for secondary specialist care.

Secondary care is the care patients receive in hospitals. This care may be planned; in the form of surgery, a medical appointment, test or screening organised by referral through a primary care professional. Or secondary care may be unplanned, in the form of emergency care.

4.2 The Health Improvement Network database

4.2.1 THIN database background

The Health Improvement Network (THIN) database is a large primary care database covering approximately 6% of the UK population. Nearly 600 general practices contribute data to THIN from across the UK. THIN contains information on over 12 million patients, with nearly 4 million active patients. The development of THIN began when GPs started to go paperless; switching from paper medical records to computerised medical records.

Computers were introduced in the early 1990s in response to a new General Medical Council (GMC) contract, which had an element of payment for performance.

At the point of joining THIN all electronic records held by the practice will be downloaded by IMS Health Intelligence Applied (the company that owns THIN), in an initial full data collection. For some practices electronic records date back to the late 1980s when computers were first introduced to primary care. After the initial full data collection, data is then downloaded by IMS Health on a monthly basis, so as to not disrupt the daily running of the practice. Data collected by THIN is anonymised and assessed for quality before being made available for research.

There is another primary care database available in the UK called Clinical Practice Research Datalink (CPRD), formerly known as General Practice Research Database (GPRD). Like THIN, CPRD contains primary care medical records from Vision practices dating back to the 1980s right up to the current date. Since THIN and CPRD utilise data from practices using the VISION software there is some overlap of data from practices in the two databases.

4.2.2 THIN data structure

THIN data made available for research is divided into seven main categories: Patient records, Therapy records, Medical records, Additional Health Data records, Postcode Variable Indicators, Consultation records, and Staff records. Figure 4.1 details the information each file category contains. In addition to these seven main data files there is one overall data file that contains basic information on each practice in THIN.

In the medical, therapy, and additional health data (AHD) records the patient's medical information is recorded using coding systems. For diagnoses and symptoms the coding system used is Read codes. Read codes were developed by Dr James Read in the 1980s (60). The codes are hierarchical from left to right and consist of up to seven alphanumerical characters. The Read codes are divided into major categories, and sub-divided into branches until specific "leaf" concepts are reached. The main branches of the Read coding and classification system are displayed in Table 4.1, codes for diabetes will appear under the main branch of; C – Endocrine, nutrition, metabolic, and immunity disorders. Read codes can either be recorded using a broad branch term or they can be recorded specifically using a leaf concept. For example Read codes for diabetes will all be coded within the "Endocrine, nutrition, metabolic, & immunity disorders" major

Figure 4.1: Description of the structure of the THIN database and the content within each main file type

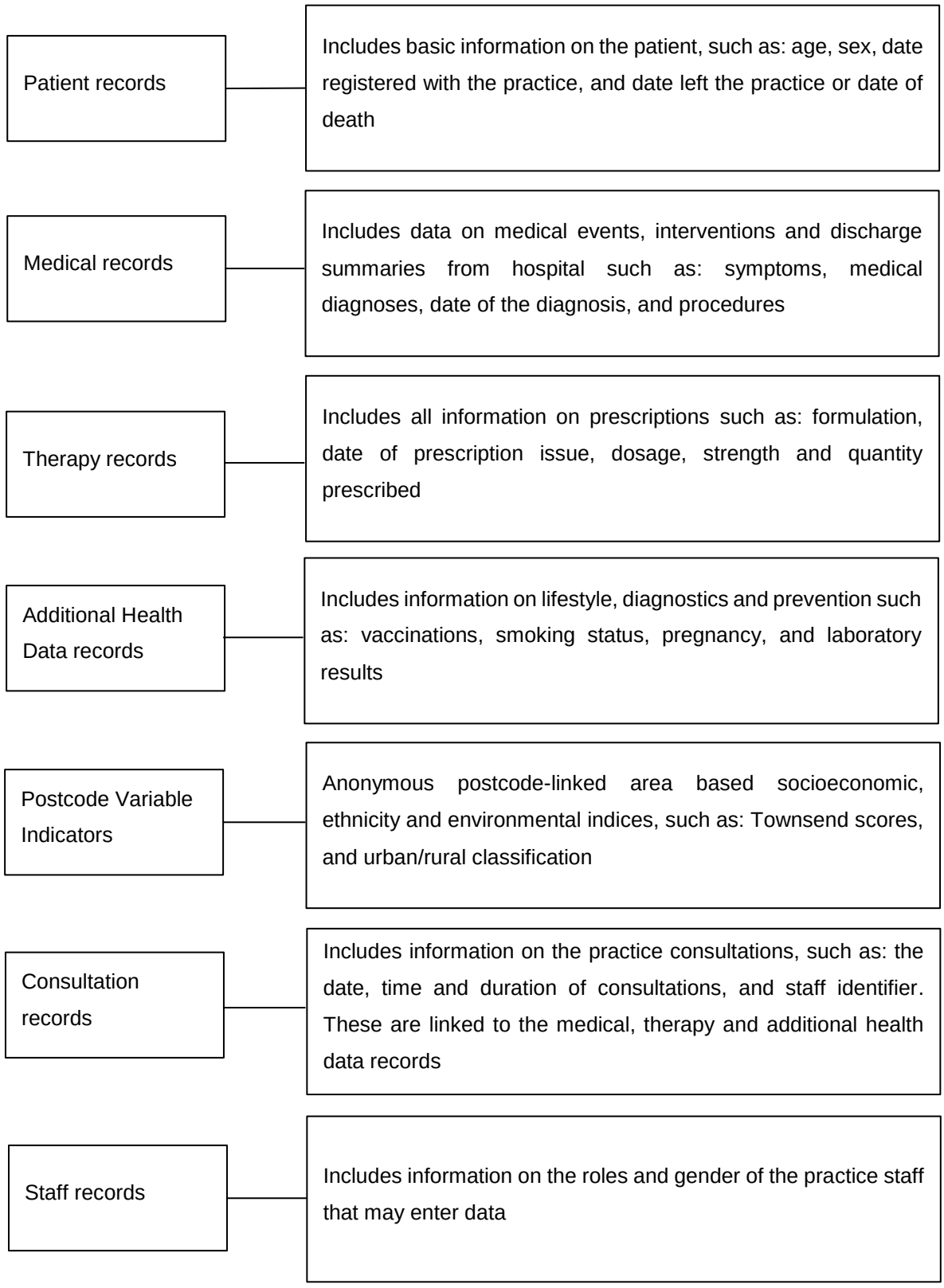


Table 4.1: Showing the first chapter of the hierarchical Read classification system

0	Occupations
1	History & symptoms
2	Examination & signs
3	Diagnostic procedures
4	Laboratory procedures
5	Radiology & physics in medicine
6	Preventative procedures
7	Operations, procedures, & sites
8	Other therapeutic procedures
9	Administration
A	Infectious & parasitic diseases
B	Neoplasm
C	Endocrine, nutrition, metabolic, & immunity disorders
D	Diseases of blood & blood forming organs
E	Mental disorders
F	Nervous system & sense organ diseases
H	Respirator system diseases
J	Digestive system diseases
K	Genitourinary system diseases
L	Complications of pregnancy, childbirth, & the puerperium
M	Skin & subcutaneous tissue diseases
N	Musculoskeletal & connective tissue diseases
P	Congenital anomalies
Q	Perinatal conditions
R	Symptoms, signs, & ill-defined conditions
S	Injury & poising
T	Causes of injury & poisoning
U	External causes of morbidity & mortality
Z	Unspecified conditions

category, with sub themes for diabetes diagnoses, and related conditions such as diabetic nephropathy. A diagnosis of type 1 diabetes mellitus may be recorded broadly using a Read code such as “C10..00 – Diabetes mellitus”. Alternatively it may be recorded more specifically using a Read code such as “C108.12 – Type 1 diabetes mellitus”. Read codes are used within both the medical records and AHD records in THIN.

The Additional Health Data (AHD) records contain another coding system alongside the Read codes called AHD codes. Unlike Read codes these do not have a hierarchical structure and were developed by the data providers to be used within THIN. AHD codes are used for: medical tests, vaccinations, and recording patient data such as height and weight or smoking status. There are two parts to the coding system; the first is the code identifying what is being recorded and the second is the information being recorded. Not all AHD codes will have additional data related to the code but if there is related

information it is recorded in one of six data fields. For example, the AHD code for height is: 1005010100, and the patient's height is recorded in meters within data field one.

The therapy records contain information on all prescriptions issued by the practice and these are recorded using drug codes. The drug codes in THIN are linked to the chapters of the British National Formulary (BNF) (14), which makes searching for prescriptions straight forward. All therapies prescribed for diabetes mellitus will be linked to BNF Chapter 6: Endocrine system, Sub-section 6.1: Drugs used in diabetes.

4.3 Identifying cases, characteristics and confounders

In 2012 there were 567 general practices contributing date to THIN from England, Wales, Scotland and Northern Ireland. With so much data to search, over 4,000 data files, a systematic approach to identify cases, characteristics, and confounders is needed. As stated in Section 4.2.2 the data is structured in such a way that each file contains different information, although there is some overlap between where certain information can be recorded. In particular, there is overlap between the medical records and the AHD records and this overlap needs to be considered when searching for cases and covariates.

Identifying cases, or patients with the diagnosis, symptom, prescription, test or referral of interest, takes a number of steps. Firstly, with clinical advice, all the terms, synonyms, and abbreviations for the outcome of interest are compiled and these terms are searched for in the relevant code book. Once an initial list of codes related to the outcome is identified then stem codes are searched to identify any other possible codes that may have been missed. For example; one of the stem codes of diabetes mellitus is C10. Any unrelated codes are excluded, again under clinical guidance. This is an iterative process (61).

Once the final list of codes related to the outcome is identified then the relevant practice records are searched, this is done using a loop. Continuing with the example of searching for a diagnosis of diabetes mellitus; the relevant practice files would be the medical records and AHD records. For each practice in turn the medical and AHD records would be searched for Read codes that appear on the diabetes code list, all records identified would then be extracted and saved into a separate data file.

The process for identifying patients that have received a specific prescription is very similar to identifying cases. The only difference being that a list of prescription codes or BNF chapter headings will be used instead of a Read code list and the therapy records will be searched instead of the medical and additional health data records.

4.3.1 Data quality

The THIN database is very large and broadly representative of the UK population but size itself does not make the data recorded of good quality. For researchers utilising this data source to be confident that their results are valid, the data recorded must be of good quality. Two markers used by THIN to assess the quality of data recorded by a practice are: the Acceptable Computer Usage (ACU) date and the Acceptable Mortality Reporting (AMR) date.

The AMR date is produced by THIN and is based on comparing mortality rates within each practice to the rest of the UK (62). For permanently registered patients; the observed yearly number of deaths recorded for each THIN practice was compared to the expected number of deaths for that practice. The observed number of deaths was calculated from the practice records each year. The age and gender standardised expected number of deaths for each practice was calculated by multiplying national annual age and sex specific death rates by the practice person time in each age and sex stratum. A standard mortality ratio (SMR) was then calculated by dividing the observed number of deaths by the expected number of deaths for each practice. Death reporting becomes closer to expected as the SMR approaches one. A THIN Acceptable Mortality Reporting date was then set as the year at which the practice's death reporting appeared to be complete based on visual inspection (62).

ACU date is defined as the date at which the practice is consistently recording, on average at least two therapy records, one medical record, and one additional health data record per patient per year (63). For each of the therapy, medical, and additional health data records, the average number of records per year was calculated by dividing the total number of health records by the number of active, permanently registered patients in the practice. Only patients without missing information on age and gender were included as active patients (63).

Excluding data recorded before the practice AMR and ACU date will make the data included in any study of higher quality.

4.3.2 Strength and Limitations of THIN

4.3.2.1 Strengths

THIN is a large primary care database with over 12 million patients of which nearly 4 million active patients. It captures real life, real time data from primary care. This means that older patients, patients with complex comorbidities or vulnerable patients that would normally be excluded from randomised controlled trials are included. The data being captured in real time means that there is no recall bias as everything is recorded during the consultation. Including a complete list of all prescriptions issued by each practice, captured automatically as they are prescribed to the patient.

The majority of people usually resident in the UK are registered with a GP and THIN has been shown to be largely representative of the UK population (64–66). This means that studies conducted using THIN data will be representative of the UK population and results could be used to inform public health policy or provide guidance to GPs.

Due to the nature of THIN, research that would otherwise be too costly or present ethical difficulties can be conducted. For example cohort studies needing a long follow-up period could be conducted using THIN with relative ease. Also, studying relatively rare exposures or rare outcomes, such as congenital malformations, is possible in THIN because of the sample size available. Another area where data from THIN provides an excellent opportunity for research is when examining effects of drug treatment in pregnancy. This is difficult otherwise for various reasons.

4.3.2.2 Limitations

As with all data sources there are some limitations to THIN primary care database. THIN was not created for research purposes rather, it is clinical data entry system built for patient management. This means that GPs are likely to only record information that has clinical relevance or will aid the care of their patients. For example, patients that appear to be of normal weight may be less likely to be weighed than overweight or obese patients leading to missing data on weight and body mass index (BMI). Also, if patients do not engage with the GP then there will be limited data available on them.

Secondly, there is no prescription compliance/adherence data recorded in THIN. From THIN it is possible to see that a patient has been issued a prescription by a GP, but it is not possible to know whether the patient has taken the medication as prescribed or even

if they have filled the prescription. This is drawback in studies that are researching non-compliance and for studies examining the effect of drug treatment.

Thirdly, information on patients is only available for as long as they are registered with the same THIN practice. If a patient deregisters with the practice or registers with another practice, then they are lost to follow-up. Even if the patient registers with a different THIN practice there is no way to link their records from the old practice.

4.4 Motivation for using THIN

THIN is a very large database containing medical records from general practices in England Scotland, Wales, and Northern Ireland. THIN has electronic medical records from over 12 million patients, of which nearly 4 million are active patients. There are a number of reasons why THIN was chosen as the data source for this thesis; studying pregestational diabetes in pregnancy.

Firstly, pregnancy is well recorded in primary care. Most women will consult their general practitioner upon first discovering they are pregnant and will attend at 6 weeks postpartum for a check-up. Also, there is an established pregnancy cohort of nearly 600,000 pregnancies within THIN; in the next chapter I will discuss the development of the pregnancy cohort. The size of the sample will allow me to study the effects of diabetes on relatively rare outcomes.

Secondly, diabetes is a life changing condition with clear diagnostic criteria meaning it will be well recorded in THIN. This means that I will be able to reliably select women with and without exposure to diabetes in pregnancy from the same sample population. Unlike the majority of the current literature, which selects women with diabetes during pregnancy from hospitals and compares the rate of adverse outcomes in women with diabetes to the national figures.

Finally, the majority of the UK population is registered with a GP, meaning THIN data is more representative of the UK population than hospital or clinical trial data. A number of studies have shown that THIN is representative of the general population in terms of demographic and clinical features. In particular the prevalence of diabetes in THIN has been shown to be very similar to national rates (64).

4.5 Summary

In this chapter I have briefly described the national health and primary care systems in the United Kingdom. I have also described the background and structure of The Health Improvement Network database (THIN) as well as identifying its strengths and limitations of.

In the next chapter I will describe the development of the pregnancy cohort used for this PhD and how women with pregestational diabetes were identified.

Chapter 5 Developing the pregnancy cohort

In the previous chapter I introduced THIN, the database which was used for this PhD. In this chapter, I introduce how the cohort of pregnant women with and without pregestational diabetes mellitus was identified in THIN. To start with I describe the algorithm developed for identifying pregnancies, before briefly explaining how mothers and children are linked. Lastly, I provide details on the algorithms used to firstly identify pregnant women with diabetes mellitus, and secondly to classify whether the women have type 1 or type 2 diabetes.

5.1 Identifying pregnancies and mother-child pairs

5.1.1 Identifying pregnancies in THIN

Pregnancy and child birth are important clinical outcomes, and as such are highly likely to be recorded in primary care and therefore captured in THIN. GPs can record pregnancies and deliveries in a number of ways, and to ensure that all pregnancies were identified an algorithm was developed by Drs Petersen and McCrea. The algorithm is described as follows.

Women are identified as pregnant via Read and AHD codes for recording:

- Last menstrual period;
- Delivery date estimation;
- Pregnancy;
- Antenatal record;
- Postnatal data;
- Linkage to a child.

To ensure that the pregnancies identified were genuine pregnancies and not, for example, medical history mistakenly recorded with a current date, a quality criteria was applied. For a pregnancy to be eligible to be included in the quality controlled pregnancy cohort, there must be at least two different types of evidence to confirm the pregnancy. For example, a pregnancy with both a delivery record and an antenatal record would be included in the quality controlled pregnancy cohort. However, a pregnancy with only an

estimated delivery date would be excluded from the quality controlled pregnancy cohort as this pregnancy may not have been completed.

In cases where the only evidence of a pregnancy are the last menstrual period date and antenatal records, further evidence was required before the pregnancy would be included in the quality controlled pregnancy cohort. These additional criteria are:

- The last antenatal record must be at least 105 days after the estimated pregnancy start date;
- And the women must have no other pregnancy record with an estimated delivery date within 280 days, either before or after, of the current pregnancy.

After the quality control criteria had been applied there were a total of 586,312 pregnancies identified in THIN from 420,234 women. From this point forward the cohort of all quality controlled pregnancies identified will be referred to as “THIN pregnancy cohort”.

5.1.2 Identifying mother-child pairs in THIN

THIN database is supplied with a variable called “famnum”, or family number, which identifies people who live at the same address. As this variable is based on the first line of the address, it is possible that units within tower blocks or university residencies will be identified as having the same address, and thus all residents will have the same family number when they register with a GP. To create links between the mother and child pairs the family number was used along with additional criteria.

The first criterion was to drop mother and child pairs where we would not have the full pregnancy or the link would be implausible. This included dropping pairs where (i) the mother was registered after the child’s birthday, (ii) the child was registered more than six months after the estimated delivery date, or (iii) the child was registered after six months of age. The second phase of mother-child linkage checking concentrated on instances where there were multiple mothers to a single child. In these instances, the most plausible mother-child linkage was identified and retained. The mother-child relationship was dropped if (i) the months of birth and delivery did not match, (ii) the child was registered before the estimated delivery date, or (iii) if the child transferred out of the practice before the estimated delivery date.

The cohort of mothers linked to a child only includes singleton pregnancies as the prevalence of apparent multiple births identified in THIN was much higher than the national average.

After the mother-child linkage criteria were applied, the cohort included 354,053 mother and child pairs with 270,462 mothers. From this point forward the quality controlled mother-child linked cohort will be referred to as “THIN mother-child linked cohort”.

5.2 Developing the study cohort

5.2.1 Inclusion criteria

A woman’s data was only eligible to be included in the study cohort for this PhD after the practice had met data quality criteria as defined by the latter of the Acceptable Computer Usage (ACU) date (63) and the Acceptable Mortality Reporting (AMR) date (62). See THIN data Chapter 4, Section 4.3.1 for more details on the ACU and AMR dates.

Once the practice data had met the inclusion criteria, each pregnancy was assessed for eligibility using the criteria below:

- The mother must be between 16 years and 55 years old at the start of the pregnancy;
- Delivery of the pregnancy must occur between 1st January 1995 and 31st December 2012;
- And the mother must be permanently registered with a practice.

Women were identified as being permanently registered with a practice via the patient flag (patflag) variable. Only those with a patflag entry of A – “Acceptable record” or C – “Acceptable: transferred out dead without additional death information” are deemed to be permanently registered and are eligible for inclusion.

The cohort of pregnant women identified for inclusion after applying both the data quality and the additional criteria made up the cohort that will be referred to as “the pregnancy cohort” from this point forward. The cohort of women linked to a child from within the pregnancy cohort will be referred to as “the mother-child linked cohort” from this point forward.

5.2.2 Identifying and defining diabetes mellitus in THIN

The medical records of women meeting the inclusion criteria for the pregnancy cohort as detailed in Section 5.2.1 were then screened for information related to diabetes mellitus. With clinical input, Read code, AHD code, and prescription code lists were developed for identifying diabetes mellitus. Each code list was developed using the methods detailed in THIN data Chapter, Section 4.3. The final code lists developed for identifying diabetes mellitus are presented in Appendix II. Table 5.1 - Table 5.3 respectively, show the five most frequently used Read codes, AHD codes, and prescription codes in THIN database. The frequency column in each table shows the number of times the code has been used in the cohort of pregnant women.

Table 5.1: The five most frequently recorded diagnostic or monitoring Read codes for diabetes mellitus among pregnant women

Read code	Description	Frequency
9N1Q.00	Seen in diabetic clinic	47,077
9OL..00	Diabetes monitoring admin.	33,187
66A..00	Diabetic monitoring	31,637
42W..00	Hb.A1C – diabetic control	30,172
66AS.00	Diabetic annual review	28,674

Table 5.2: The five most frequently recorded diagnostic Additional Health Data codes for diabetes mellitus among pregnant women

AHD code	Description	Frequency
1001400140	Hb A1C – Diabetic control	188,176
1009100000	Diabetes annual check	31,169
1001400327	Diabetic retinopathy screening	25,588
1009111000	Diabetes current status	21,393
1009120000	Diabetes insulin dosage	701

Table 5.3: The five most frequently recorded prescription codes for diabetes mellitus therapies among pregnant women

Prescription code	Generic name	Frequency
97087998	Metformin 500mg tablets	165,197
96283998	Gliclazide 80mg tablets	48,928
98198998	Insulin aspart 100u/ml cartridges	44,411
87054998	Metformin 500mg modified-release tables	29,709
91509998	Insulin aspart 100units/ml pens	29,561

In total, there were 638 Read codes identified and included in the Read code list, as being related to either diagnosing or monitoring diabetes mellitus. There were 565 prescription codes identified for the treatment of diabetes mellitus, and five AHD codes were identified as being related to diagnosed diabetes mellitus. There were additional AHD codes related to tests for diagnosing diabetes mellitus and not diagnosed diabetes mellitus that were removed, for example AHD code 100140084 – “Glucose tolerance test”.

The medical and AHD records of pregnant women included in the pregnancy cohort were then searched for Read codes on the developed Read code list. Therapy records were searched for prescription codes on the developed list. Finally, AHD records were searched for one of the five AHD codes for diagnosed diabetes mellitus. All related records were extracted from THIN before further steps to confirm a diagnosis of diabetes and classify women as having type 1 or type 2 diabetes were taken.

5.2.2.1 Defining pregestational diabetes mellitus

To confirm the diagnosis of diabetes mellitus, I set the following criteria. A woman must have in her records at least one diabetic related Read code in combination with either:

- A record for a diabetic related prescription code;
- A record for a diabetic related AHD code;
- Or another diabetic related Read code.

To then define pregestational diabetes the first two diabetic records must be recorded prior to the start of pregnancy. Women who had a single record of diabetes (be it a Read, AHD or prescription code) or, multiple prescription records without a diabetic specific Read code were excluded from the pregnancy cohort as their diabetic status could not be verified (see Figure 5.1).

5.2.3 Classifying diabetes mellitus in THIN primary care database

Once I had identified the women with confirmed pregestational diabetes, the next step was to classify women as type 1 or type 2 diabetic. This turned out to be a complicated process, with much discussion before the final classification system was decided upon.

5.2.3.1 Initial classification system

I initially started using a classification system outlined by Massó González *et al* (3). This paper assessed the trends in the prevalence and incidence of diabetes mellitus in the general population, using THIN. They classified diabetes type using three variables:

1. Whether the person had a type specific Read code in their records;
2. Age at the first diagnosis of diabetes;
3. And the diabetic therapy prescriptions they received.

The first variable identified whether a type specific Read code appeared in the medical records, within one year of the first diabetes mellitus record. A type specific Read code contains information on the type of diabetes the person was diagnosed with. An example of a type specific Read code is: "C108.12 - Type 1 diabetes mellitus", which indicates that the person had type 1 diabetes. The second variable, age at first diagnosis, identified the age at which the first record of diabetes mellitus appeared in the person's medical records. The final variable, diabetic prescriptions received, captured whether the person had received one or more insulin prescriptions and whether the person had received at least a year's worth of prescriptions of oral antidiabetics (3).

The algorithm Massó González *et al* then used to classify diabetes mellitus type was:

Type 1 diabetes:

- Type 1 specific Read code within one year of the first diagnosis;
- Or no type specific Read codes, aged less than 35 years at diagnosis, received one or more prescriptions for insulin, and less than a years' worth of oral antidiabetics.

Type 2 diabetes:

- Type 2 specific Read code within one year of the first diagnosis;
- Or no type specific Read codes and no diabetic drug therapy prescriptions;
- Or no type specific Read codes and at least a year's worth of oral antidiabetic prescriptions.

When I applied this algorithm to my pregnancy cohort, there were a large number of women that were left unclassified. This was mainly because (i) they had type specific Read codes for both type 1 and type 2 diabetes in the first year after diagnosis, (ii) they

had no type specific Read codes, and had received less than a years' worth of oral antidiabetics, or (iii) they had type 1 specific Read codes in the first year after diagnosis but had not received any prescriptions for insulin. Therefore, to classify the pregnancy cohort more completely I needed to adapt the classification system used by Massó González *et al*.

5.2.3.2 Definition of characteristics used in the final classification algorithm

The final diabetes type classification algorithm was built on four variables including the three used in the algorithm defined by Massó González *et al* with some minor alterations and one additional variable, as detailed below.

The variable I introduced identified the timing of the first record of diabetes, this was to enable differentiation between prevalent and incident cases of diabetes at the time of registration with the practice. A prevalent case of diabetes was defined as someone who had a first record of diabetes within the first nine months of registering with a practice, and an incident case of diabetes was defined as someone who had a first record of diabetes after nine months of registering with a practice. A period of nine months after registration was used to separate prevalent and incident diabetes cases based on a paper by Mamtani *et al* (67).

Of the three variables used by Massó González *et al*, the only one that remained unchanged was the age at the first record of diabetes. This variable remained as a binary indicator of whether or not a person was over the age of 35 years old at diagnosis. The remaining two variables: type specific Read codes, and antidiabetic therapy prescription records, were altered slightly for my diabetes classification algorithm.

The type specific Read code variable was expanded into three categories: type 1 diabetes specific codes only, type 2 diabetes specific codes only, and an "unclear" type category. The "unclear" category included: women with both type 1 and type 2 Read codes, and women with no type specific Read codes. Unlike, Massó González *et al*, I lifted the time constraint on the recording of diabetes type specific Read codes, so that type specific Read codes could be recorded at any time and not only just in the first year after diagnosis.

Table 5.4: The final algorithm for classifying the type of diabetes mellitus using electronic medical records

	Type	Treatment	Case	Age	N (%)
Type 1				**Total**	**1,361**
	T1 only	Insulin only			773 (57)
		Insulin + OAD<6m			80 (6)
	T2 only	Insulin only	Incident	<35	18 (1)
				≥35	3 (0.2)
			Prevalent	<35	11 (0.8)
	Unclear[§]	Insulin only	Incident	<35	110 (8)
				≥35	19 (1)
			Prevalent	<35	264 (19)
		Insulin + OAD<6m	Incident	<35	42 (3)
				≥35	5 (0.4)
			Prevalent	<35	37 (3)
Type 2				**Total**	**2,016**
	T1 only	Insulin + OAD≥6m			125 (6)
		OAD≥6m			1 (0.05)
		No treatment			1 (0.05)
	T2 only	Insulin only	Prevalent	≥35	9 (0.4)
		Insulin + OAD<6m			49 (2)
		Insulin + OAD≥6m			443 (22)
		OAD<6m			34 (2)
		OAD≥6m			71 (4)
		No treatment			39 (2)
	Unclear[§]	Insulin only	Prevalent	≥35	33 (2)
		Insulin + OAD<6m	Prevalent	≥35	1 (0.05)
		Insulin +OAD≥6m			208 (10)
		OAD<6m			187 (9)
		OAD≥6m			287 (14)
		No treatment			528 (26)
Unclassified				**Total**	**62**

Type	Treatment	Case	Age	N (%)
T2 only	Insulin only	Unknown		7 (11)
Unclear	Insulin only	Unknown		40 (65)
Unclear	Insulin + OAD<6m	Unknown		15 (24)

§ - Type 1 and type 2 diabetes mellitus codes or Non-specific codes; T1 - Type 1 Diabetes Mellitus; T2 - Type 2 Diabetes Mellitus; OAD - Other antidiabetics.

The diabetic therapy prescriptions variable was also expanded so that it had six categorises insulin only, insulin and short term oral antidiabetics (OAD), insulin and long term OAD, short term OAD, long term OAD, and no treatment prescriptions. Short term OAD prescriptions were defined as having less than six months of cumulative prescriptions recorded, and long term OAD prescriptions were defined as having at least six months of cumulative prescriptions recorded.

5.2.3.3 Final classification algorithm

The different combinations of the four variables described above define the diabetes mellitus type classification algorithm used in this PhD. Table 5.4 shows the different combinations of the four variables and the resulting classification as either type 1 or type 2 diabetes mellitus, or in a few cases unclassified diabetes type (68).

In general, the algorithm classifies people as type 1 diabetic if they had prescriptions for insulin with or without short term OADs, and are under the age of 35 years at diagnosis. It classifies people as type 2 diabetic if they had prescriptions for OADs alone, long term OADs in combination with insulin, or no prescriptions, and if they are over 35 years of age at diagnosis.

Women with an unclassified diabetes status were excluded from the final pregnancy cohort.

5.3 Identification of maternal characteristics

For both women with and without diabetes mellitus maternal characteristics were extracted from THIN database on: age, body mass index (BMI), diabetic therapy prescriptions, blood pressure, glycaemic control, smoking status, alcohol dependence, and Townsend deprivation score.

5.3.1.1 Maternal age and BMI

Maternal age was defined as age at the start of the pregnancy.

To define BMI, maternal height and weight were extracted from THIN AHD records. Initially, maternal weight was extracted from 12 months prior to the pregnancy and up to the pregnancy start date, ignoring any records taken during previous pregnancies. For women without a weight recorded in the 12 months prior to pregnancy, additional weight records were extracted until six weeks gestation. Any values lying outside the top or bottom one percentile of the population distribution for height and weight were considered as outliers and recoded to missing. For women with multiple height measurements during adulthood (after the age of 16), a single height measurement was randomly selected. The weight measurement nearest to the pregnancy start date was taken. BMI was then defined as weight (kilo grams, kg) divided by height (square meters, m^2). I also created an overweight indicator for BMI≥25kg/m^2.

5.3.2 Antidiabetic therapies

For women with pregestational diabetes mellitus, all prescriptions for diabetic therapies were extracted during pregnancy. The prescriptions were categorised into insulin, including all types of long and short acting insulins; biguanides; metformin being the only available one; sulphonylureas; and other therapies. Women may be issued prescriptions from more than one drug therapy category.

5.3.2.1 Blood pressure

Blood pressure measurements were extracted from THIN AHD records. Values were converted to millimetres of mercury (mmHg) where necessary, and any outliers were identified and set to missing as detailed below. For diastolic blood pressure, values were considered outliers if they were below 50mmHg or above 130mmHg. For systolic blood pressure, values were considered outliers if they were below 70mmHg or above 220mmHg.

The blood pressure value recorded nearest to pregnancy and within the 12 months prior to the pregnancy start date was taken. For women without a blood pressure value recorded in the 12 months prior to pregnancy, additional blood pressure values were extracted from the start of pregnancy up to six weeks gestation. The same data cleaning process was applied and the blood pressure value recorded nearest to the start of

pregnancy was taken. If women had multiple blood pressure values recorded on the same day then the mean value was taken.

5.3.2.2 Glycaemic control

For both women with and without pregestational diabetes mellitus, glycaemic control at the start of pregnancy was extracted from THIN using Read codes for glycated haemoglobin (HbA_{1c}), glucose tolerance test, fasting plasma glucose, and random plasma glucose. For each type of glucose measurement any values lying outside the top or bottom one percentile of the population distribution were considered as outliers and set to missing. For each blood glucose measurement, the value recorded nearest to the start of the pregnancy date and within the previous 12 months was taken.

Hyperglycaemia in the 12 months before pregnancy was identified as when a woman had HbA_{1c} test>48mmol/mol, fasting glucose test>7mmol/l, or random glucose test>9mmol/l in the 12 months prior to pregnancy.

5.3.2.3 Smoking status

Smoking status was recorded in the AHD records, and was extracted from THIN. To incorporate smoking history, if a woman has a record indicating she is a current or former smoker, and at a later date has a record indicating she is a non-smoker, the later record will be set to ex-smoker. This is to ensure smoking status continuation. For women with multiple records prior to pregnancy, the smoking status recorded nearest to the start of the pregnancy was taken. Smoking status may change between pregnancies; therefore; for each pregnancy the smoking status recorded nearest to the start of that pregnancy was taken.

5.3.2.4 Alcohol dependence

The amount of alcohol consumed per week and problematic alcohol drinking are recorded within the medical and AHD records in THIN, all related records were extracted. Women who consumed 35 or more units of alcohol per week at any time in the three years prior to pregnancy were identified as having alcohol dependence.

5.3.2.5 Townsend deprivation score

Townsend deprivation score quintiles (69) will be used to measure social deprivation; these are provided in THIN and are linked to postcode. The Townsend deprivation score

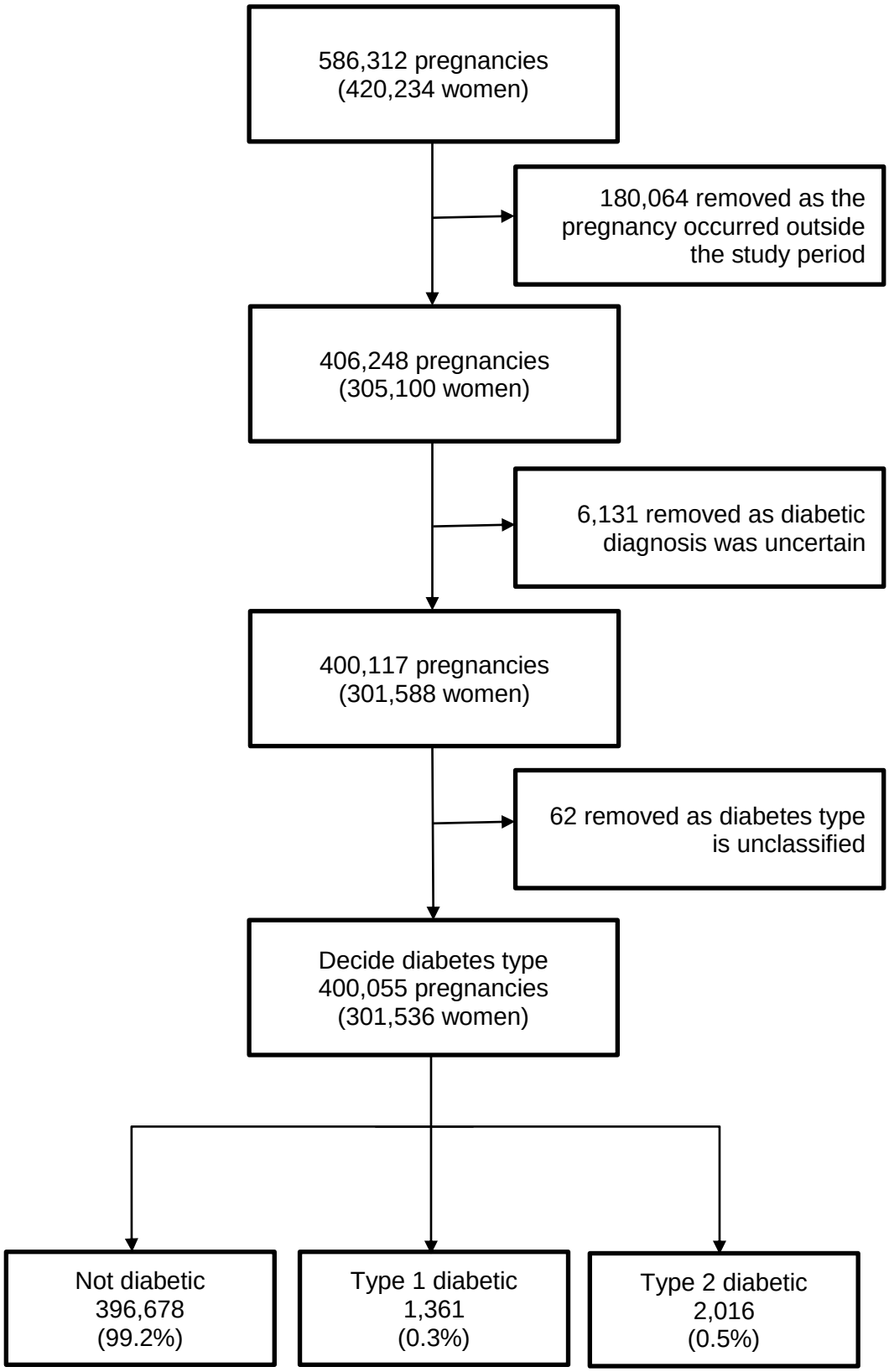
is derived using information from the 2001 UK census on unemployment, overcrowding, car ownership, and home ownership (69). The scores are grouped into five quintiles, from one (the least deprivation) to five (the most deprivation). Outliers were set to missing. For women with multiple Townsend deprivation scores recorded prior to pregnancy, the one recorded nearest to the pregnancy was taken.

5.3.2.6 Ethnicity

Maternal ethnicity was extracted from THIN using Read codes. After manual review, all identified codes were categorised into five ethnic groups: white, black, Asian, mixed, or other according to the five-category Office of National Statistics (ONS) 2001 UK census classification (70).

For women with a single ethnicity code or multiple ethnicity codes from the same ethnicity category, their ethnicity classification was straight forward. The ethnicity classification for women with multiple ethnicity codes from more than one ethnicity category was a little more complex. These women were classified according to whether they had a most common ethnicity category. For example, a woman may have three ethnicity codes of which two are in the white ethnicity category and one in another ethnicity category. For this woman the most common ethnicity category is white and she would be classified as having white ethnicity. For women with multiple ethnicity codes from more than one ethnicity category without a most common ethnicity category, the most recently recorded ethnicity category was assigned.

Figure 5.1: Flow diagram describing the identification of the pregnancy cohort



5.4 Description of the Pregnancy Cohort

There were 586,312 pregnancies identified in THIN database using the algorithm described in Section 5.1.1. Of which 180,064 pregnancies were removed because they did not meet the inclusion criteria for the pregnancy cohort (Section 5.2.1). A further 6,131 pregnancies were removed because I could not confirm a diabetic diagnosis for the mother, either because she only had one record of diabetes in her medical records or because she had received a diabetic related prescription without any diagnostic Read codes present in her medical records (Section 5.2.2). Finally, 62 pregnancies were removed as the type of diabetes of the mother could not be classified (Section 5.2.3.3) (Figure 5.1).

The final pregnancy cohort consists of 400,055 pregnancies to 301,536 mothers (Figure 5.1). Pregestational diabetes affected 3,377 (0.8%) pregnancies in the final pregnancy cohort. Of these 1,361 (0.3%) were affected by type 1 diabetes and 2,016 (0.5%) were affected by pregestational type 2 diabetes.

5.5 Summary

In this chapter, I have described in detail how pregnant women and women with diabetes were identified in THIN. I have also presented the algorithm developed to classify whether pregnant women with diabetes have type 1 or type 2 diabetes.

In the next chapter, I will be exploring the pregnancy cohort in more detail via my first study.

Chapter 6 Type 1 and Type 2 Diabetes Mellitus in Pregnancy

6.1 Introduction

Diabetes mellitus diagnosed prior to the start of pregnancy is one of the commonest chronic conditions affecting pregnancy (28). Pregestational type 1 and type 2 diabetes in pregnancy is associated with an increased risk of adverse outcomes for mother and child. Management of diabetes prior to and during pregnancy aims to maintain strict glycaemic control, thus reducing the risks of adverse pregnancy outcomes.

In the general population the prevalence and incidence of diabetes has increased over recent years (3). A study by Massó González *et al* (3) conducted in THIN found that the prevalence of diabetes increased from 2.8% to 4.3% between 1996 and 2005, an increase of over 50%. Whilst the incidence of type 1 diabetes remained relatively constant throughout the study period; approximately 0.13 per 1,000 person-years. The incidence of type 2 diabetes increased from 2.60 per 1,000 person-years to 4.31 between 1996 and 2005, a 66% increase in a decade (3).

The increasing prevalence of diabetes in the general population has translated to an increase in prevalence of diabetes in the pregnant population. There have been a number of studies examining the temporal trends in the prevalence of diabetes in pregnancy (71–73,34,74–77). Three USA based studies (72,73,76) investigated the temporal trends using electronic health records from hospitals and health insurers all found that the prevalence of diabetes in pregnancy increased. Two of the American studies (73,76) were unable to differentiate between pregestational diabetes types 1 and 2; Bardenheier *et al* (73) found that pregestational diabetes in pregnancy increased from 0.65 per 100 deliveries to 0.89 per 100 deliveries between 2000 and 2010. Whilst Lawrence *et al* (76) found the prevalence of pregestational diabetes increased from 0.81 to 1.82 per 100 births between 1999 and 2005. The only American study (72) which estimated the prevalence of diabetes in pregnancy separately for type 1, type 2, and gestational diabetes found an overall prevalence of 4.3 per 100 deliveries across the study period between 1994 and 2004. Albrecht *et al* (72) found the prevalence of type 1 diabetes increased from 0.24 to 0.33 per 100 deliveries between 1994 and 2004 and the

prevalence of type 2 diabetes increased from 0.09 to 0.42 per 100 deliveries between 1994 and 2004.

Two studies in Australia located in; Victoria (71) and the Torres Strait Islands (74), again found that the prevalence of diabetes in pregnancy increased. Abouzeid *et al* (71), were unable to calculate separate estimates for type 1 and type 2 diabetes and found the prevalence of pregestational diabetes increased from 0.4% to 0.6% between 1999 and 2008. Whereas, Falhammar *et al* (74), only studied women with type 2 diabetes in pregnancy and found the prevalence of pregestational type 2 diabetes increased from 0.8% to 4.6% between 1999 and 2005/2006.

One study, by Bell *et al*, on the temporal trends in the prevalence of pregestational diabetes conducted in the northern region of England (34) found a 50% increase in the prevalence of pregestational diabetes between 1996-98 and 2002-04. The increase in prevalence was attributed to a sharp rise in the prevalence of type 2 diabetes over the study period; type 2 diabetes increased from 0.2 per 1,000 births to 1.2 per 1,000 births between 1996-98 and 2002-04. The Confidential Enquiry into Maternal and Child Health (CEMACH) also conducted in the United Kingdom estimated the national and regional prevalence of diabetes in pregnancy for one year between 1 March 2002 and 28 February 2003 (78). CEMACH found type 1 diabetes accounted for 2.7 per 1,000 of all births in England, Wales, and Northern Ireland. Whereas, type 2 diabetes affected 1.0 per 1,000 births in England, Wales, and Northern Ireland (78).

This study will allow me to initially explore and describe pregestational diabetes as recorded in THIN as well as providing the grounding and background for the rest of my thesis. The overall aims of this study are to investigate the temporal changes in the prevalence of pregestational diabetes and management.

6.1.1 Study objectives

The overall aim of this study was to investigate the prevalence of pregestational diabetes mellitus in diabetes using THIN. Specific objectives were set out to explore whether there were any differences between pregnant women with and without pregestational diabetes mellitus and whether there were any temporal changes in the prevalence of pregestational diabetes mellitus.

Three specific objectives set were:

1. To compare maternal characteristics between pregnant women with and without pregestational diabetes mellitus.

2. Investigate temporal trends in the prevalence of pregestational diabetes mellitus affecting pregnancy between January 1995 and December 2012.

3. Explore which antidiabetic therapies are prescribed to women with pregestational diabetes mellitus during pregnancy.

6.2 Methods

6.2.1 Study cohort

Each objective was studied in turn using the pregnancy cohort described in detail in the previous chapter. Briefly, the pregnancy cohort contains all women permanently registered with a THIN primary care practice, aged between 16 and 55 years with pregnancies delivering between January 1995 and December 2012. Data from each practice was only used after the acceptable computer usage (ACU) and acceptable mortality rate (AMR) dates. The ACU and AMR dates were explained in detail in Section 4.3.1.

6.2.2 Statistical methods

Objective 1 - Comparison of maternal characteristics between pregnant women with and without pregestational diabetes

To compare socio-demographic and other maternal characteristics between pregnant women with and without diabetes, summary statistics were calculated for women with type 1, type 2, and no diabetes separately. Mean and standard deviations (SD) were calculated for continuous maternal characteristics: age (years); BMI (kg/m^2); blood pressure; glycaemic control, captured through fasting plasma glucose, random plasma glucose or glycated haemoglobin (HbA_{1c}), and length of records prior to pregnancy (years). Number, percent, and 95% confidence intervals (CI) were calculated for categorical maternal characteristics: overweight ($BMI \geq 25 kg/m^2$); smoking status (coded as non-smoker, ex, and current); ethnicity (coded as white, black, Asian, mixed, and other), hyperglycaemia in the 12 months prior to pregnancy, and social deprivation measured by Townsend quintile (coded as: one most deprived to five least deprived). For women with multiple eligible pregnancies recorded during the study period a single pregnancy was selected at random for this section of the analysis.

Objective 2 - Temporal trends in the prevalence of pregestational diabetes

To investigate temporal trends in the prevalence of pregestational diabetes, the prevalence of pregestational diabetes in pregnancy was calculated by calendar year and diabetes type for all years between 1995 and 2012. The denominator for the prevalence of type 1 diabetes mellitus in pregnancy included all pregnancies with an estimated delivery date recorded within a given year. The numerator included all pregnancies to women with type 1 diabetes mellitus, with an estimated delivery date within the same calendar year. The same calculation was performed for the prevalence of type 2 diabetes in pregnancy. For this and subsequent analyses all eligible pregnancies were included. I chose to calculate prevalence and not incidence as I was interested in all pregnancies affected by diabetes and not just the first pregnancy recorded in THIN.

Previous studies using THIN have shown that as the length of time a subject is registered with a THIN practice increased, the likelihood of a diagnosis being recorded also increased. I therefore decided to conduct a sensitivity analysis to investigate whether the length of time a woman is registered with a practice prior to pregnancy affected the estimated prevalence of pregestational diabetes in pregnancy. The sensitivity analysis required recalculation of the prevalence of pregestational diabetes in pregnancy by calendar year and diabetes type having first restricted the cohort to women with a minimum length of time registered with a practice prior to pregnancy. I initially restricted the cohort to include women that had been registered with a GP one year prior to pregnancy and recalculated the prevalence. I then repeated the process restricting the cohort to women that had been registered with a GP practice prior to pregnancy for between at least two and six years, inclusively.

As well as investigating whether there were temporal changes in the prevalence of pregestational diabetes in pregnancy, I also investigated whether the prevalence of diabetes altered within maternal age and overweight category. To do this, the prevalence of pregestational diabetes was calculated within calendar year and age or overweight category, for each diabetes status separately. Maternal age was categorised as: under 35 years or 35 years and older and maternal BMI was categorised as: normal ($BMI<25kg/m^2$) and overweight ($25kg/m^2 \geq BMI$).

Objective 3 - Prescribing of antidiabetic therapies to women with diabetes in pregnancy

To investigate which antidiabetic therapies were prescribed during pregnancy, the prevalence of prescribing was calculated by diabetes type and therapy category for the calendar periods: 1995-97, 1998-2000, 2001-03, 2004-06, 2007-09, and 2010-12. For type 1 diabetic women the denominator for the prevalence calculation included all pregnancies to women with pregestational type 1 diabetes mellitus with an estimated delivery date recorded within the given calendar period, regardless of pregnancy outcome. The numerator included all pregnancies to women with pregestational type 1 diabetes mellitus receiving an antidiabetic therapy prescription during pregnancy. Each antidiabetic therapy category insulin, metformin, sulphonylureas, and other was calculated separately. The same calculation was performed for pregnant women with type 2 diabetes mellitus.

6.3 Results

The final pregnancy cohort developed consisted of 400,055 pregnancies to 301,536 women. Of which pregestational diabetes affected 0.8%. Type 1 diabetes affected 0.3% (1,361/400,055) of pregnancies and type 2 diabetes affected 0.5% (2,016/400,055) of pregnancies. The majority of women in the study cohort had a single pregnancy (75.4%) and only 0.7% of women had four or more pregnancies (Table 6.1). Women with type 2 pregestational diabetes in pregnancy were slightly more likely to have multiple pregnancies. Twenty eight percent of women with type 2 diabetes had two pregnancies compared to 20.6% of women without diabetes and 21.6% of women with type 1 diabetes in pregnancy (Table 6.1).

Table 6.1: The number of pregnancies a woman has recorded* in THIN stratified by diabetes status

	Number of pregnancies N (%)				
	1	**2**	**3**	**4 or more**	**Total**
Type 1 diabetes	1,018 (74.8)	294 (21.6)	45 (3.3)	4 (0.3)	1,361
Type 2 diabetes	1,365 (67.7)	522 (25.9)	112 (5.6)	17 (0.8)	2,016
Not diabetic	299,153 (75.4)	81,613 (20.6)	13,326 (3.4)	2,586 (0.7)	396,678
Total	301,536 (75.4)	82,429 (20.6)	13,483 (3.4)	2,607 (0.7)	400,055

*Please note: the first pregnancy recorded in THIN may not be the woman's first pregnancy

Table 6.2: Descriptive statistics for categorical maternal demographic and clinical characteristics prior to pregnancy for women with and without pregestational diabetes

		Type1		Type 2		Not diabetic		
		N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	p-value[1]
Age categorical	16-24	200 (0.3)	(0.25, 0.33)	154 (0.2)	(0.19, 0.26)	70269 (99.5)	(99.44, 99.55)	<0.001
	25-34	644 (0.4)	(0.34, 0.40)	899 (0.5)	(0.48, 0.55)	173266 (99.1)	(99.07, 99.16)	
	35-44	217 (0.4)	(0.34, 0.44)	444 (0.8)	(0.73, 0.87)	55096 (98.8)	(98.72, 98.90)	
	44+	1 (0.3)	(0.04, 2.02)	7 (2.0)	(0.96, 4.17)	339 (97.7)	(95.45, 98.84)	
Overweight	No	364 (0.4)	(0.33, 0.41)	231 (0.2)	(0.21, 0.27)	98177 (99.4)	(99.35, 99.44)	<0.001
	Yes	568 (0.6)	(0.55, 0.65)	1043 (1.1)	(1.03, 1.16)	93731 (98.3)	(98.23, 98.39)	
	Missing	130 (0.1)	(0.10, 0.14)	230 (0.2)	(0.19, 0.24)	107062 (99.7)	(99.62, 99.70)	
Ethnic group	White	575 (0.4)	(0.38, 0.45)	705 (0.5)	(0.47, 0.54)	138,871 (99.1)	(99.04, 99.14)	<0.001
	Mixed	8 (0.5)	(0.25, 0.98)	12 (0.7)	(0.42, 1.29)	1610 (98.8)	(98.11, 99.21)	
	Black	14 (0.2)	(0.14, 0.40)	54 (0.9)	(0.70, 1.20)	5806 (98.8)	(98.53, 99.09)	
	Asian	22 (0.2)	(0.13, 0.31)	158 (1.5)	(1.25, 1.71)	10626 (98.3)	(98.07 98.56)	
	Other	10 (0.2)	(0.13, 0.46)	27 (0.7)	(0.46, 0.98)	3986 (99.1)	(98.73, 99.33)	
	Missing	433 (0.3)	(0.28, 0.34)	548 (0.4)	(0.36, 0.43)	138071 (99.3)	(99.25, 99.34)	
Townsend quintile	1	239 (0.4)	(0.32, 0.41)	230 (0.4)	(0.31, 0.40)	65166 (99.3)	(99.22, 99.35)	<0.001
	2	206 (0.4)	(0.32, 0.42)	249 (0.4)	(0.39, 0.50)	55871 (99.2)	(99.11, 99.26)	
	3	204 (0.3)	(0.29, 0.38)	342 (0.6)	(0.50, 0.62)	60755 (99.1)	(99.03, 99.18)	
	4	209 (0.4)	(0.31, 0.40)	325 (0.6)	(0.49, 0.61)	58553 (99.1)	(99.02, 99.17)	
	5	151 (0.3)	(0.29, 0.40)	274 (0.6)	(0.54, 0.69)	44270 (99.0)	(98.95, 99.13)	
	Missing	53 (0.4)	(0.28, 0.48)	84 (0.6)	(0.47, 0.72)	14355 (99.1)	(98.88, 99.20)	

		Type1		Type 2		Not diabetic		
		N (%)	95% CI	N (%)	95% CI	N (%)	95% CI	p-value[1]
Smoking Status	Never	453 (0.4)	(0.32, 0.39)	681 (0.5)	(0.49, 0.57)	127267 (99.1)	(99.06, 99.17)	<0.001
	Ex	323 (0.4)	(0.32, 0.40)	493 (0.6)	(0.50, 0.60)	88756 (99.1)	(99.02, 99.15)	
	Current	280 (0.3)	(0.31, 0.39)	329 (0.4)	(0.37, 0.45)	80119 (99.2)	(99.28, 99.30)	
	Missing	6 (0.2)	(0.10, 0.47)	1 (0.04)	(0.01, 0.25)	2828 (99.8)	(99.48, 99.88)	
Hyperglycaemia[2]	No	539 (0.2)	(0.20, 0.24)	1182 (0.4)	(0.40, 0.45)	298904 (99.4)	(99.33, 99.39)	<0.001
	Yes	523 (59.6)	(55.87, 63.26)	322 (34.2)	(30.67, 37.83)	66 (6.2)	(4.62, 8.30)	

[1] P-value calculated from a chi-squared test
[2] Hyperglycaemia defined as HbA_{1c}>6.5% at the most recent test in the previous 12 months

Table 6.3: Descriptive statistics for continuous maternal demographic and clinical characteristics prior to pregnancy for women with and without pregestational diabetes

		Type 1 diabetes		Type 2 diabetes		Not diabetic		p-value[1]
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Maternal age	Years	1,062	29.5 (5.7)	1,504	31.5 (5.3)	298,970	29.0 (5.9)	<0.001
BMI[2]	kg/m^2	932	26.0 (4.7)	1,274	31.0 (7.0)	191,908	25.1 (5.2)	<0.001
Diastolic blood pressure	mmHg	924	73.9 (9.3)	1,200	77.1 (10.1)	194,069	72.7 (9.3)	<0.001
Systolic blood pressure	mmHg	926	119.4 (13.7)	1,200	122.0 (14.4)	194,379	116.5 (12.9)	<0.001
Hba1c	mmol/L	566	67.3 (21.3)	462	56.4 (20.7)	18	41.0 (12.8)	0.04
Random plasma glucose	mmol/L	179	8.4 (3.0)	360	6.8 (2.9)	17,832	4.8 (0.7)	<0.001
Fasting glucose	mmol/L	37	7.5 (2.7)	111	6.9 (2.6)	3,214	4.7 (0.5)	<0.001
Prior registration[3]	Years	1,062	3.9 (3.8)	1,504	4.4 (3.9)	298,970	3.4 (3.7)	0.037

[1] P-value from a one-way of variance test
[2] BMI: Body Mass Index
[3] Length of time registered with the GP prior to pregnancy

6.3.1 Objective one - Comparison of maternal characteristics between pregnant women with and without pregestational diabetes

Pregnant women with pregestational diabetes were: older, had higher BMI, had higher blood pressure, were more likely to have a blood glucose test prior to pregnancy, and were registered with a general practice for longer prior to pregnancy when compared to pregnant women without diabetes (Table 6.3). The mean (SD) age was 29.5 (5.7) years, 31.5 (5.3) years and 29.0 (5.9) years for pregnant women with type 1 diabetes, type 2 diabetes, and without diabetes respectively. The mean (SD) BMI was 26.0kg/m^2 (4.7), 31.0kg/m^2 (7.0) and 25.1kg/m^2 (5.2) for pregnant women with type 1 diabetes, type 2 diabetes, and without diabetes respectively. The mean (SD) length of registration prior to pregnancy was 3.9 years (3.8) for pregnant women with type 1 diabetes, 4.4 years (3.9) for women with type 2 diabetes, and 3.4 years (3.7) for pregnant women without diabetes (Table 6.3).

Pregnant women with pregestational type 1 diabetes had higher blood glucose concentrations when compared to pregnant women with type 2 diabetes. Mean (SD) HbA_{1c} concentrations prior to pregnancy were 67.3mmol/mol (21.2) for women with type 1 diabetes compared to 56.4mmol/mol (20.7) for women with type 2 diabetes. Pregnant women with type 1 diabetes were more likely to have a recorded HbA_{1c} test prior to pregnancy when compared to pregnant women with type 2 diabetes; 42% vs 23% (Table 6.3). There was a higher proportion of women with type 1 diabetes within those with hyperglycaemia in the 12 months prior to pregnancy than women with type 2 diabetes; 60% (95% CI (55.87%, 63.26%) compared to 34.2% (95% CI (30.67%, 37.83%)) (Table 6.2).

There was a higher proportion of women with type 2 diabetes within those that were: overweight, of non-white ethnicity, the most socially deprived Townsend quintile, and the oldest age groups when compared to women with type 1 diabetes in pregnancy (Table 6.2). The proportion of women with type 2 diabetes within those that were overweight was nearly twice as high as the proportion of women with type 1 diabetes; 1.1% (95% CI (1.03%, 1.16%)) compared to 0.6% (95% CI (0.55%, 0.65%)), respectively. Within those with mixed, black, Asian, or other ethnicity the proportion of women with type 2 diabetes was: 0.7%, 0.9%, 1.5%, and 0.7% respectively compared to 0.5%, 0.2%, 0.2%, and 0.2% for women with type 1 diabetes, respectively. The proportion of women with type 2 diabetes compared to the proportion of women with type 1 diabetes was twice as high

amongst those aged 35-44 years at the start of pregnancy and nearly seven times higher amongst those aged greater than 44 years at the start of pregnancy (Table 6.2).

However, there is a substantial amount of missing data on BMI or overweight, and for ethnicity, which makes the results difficult to interpret. For pregnant women with type 1 diabetes, type 2 diabetes, and no diabetes; 10%, 11% and 27% had no BMI recorded, respectively. Whereas, for pregnant women with type 1, type 2 and no diabetes; 32%, 27% and 35% had no ethnicity recorded, respectively.

6.3.2 Objective two - Temporal trends in the prevalence of pregestational diabetes in pregnancy

The prevalence of pregestational type 1 diabetes and type 2 diabetes in pregnancy increased over the study period (Figure 6.1). The prevalence of type 1 diabetes in pregnancy started at 1.58 per 1,000 pregnancies in 1995 and initially increased to a peak of 3.75 per 1,000 pregnancies in 1998. The prevalence of type 1 diabetes in pregnancy then fell slightly to 2.61 per 1,000 pregnancies in 2003 before increasing again. By the end of the study period the prevalence of type 1 diabetes in pregnancy had increased to the study peak of 4.34 per 1,000 pregnancies in 2012 (Figure 6.1).

The prevalence of type 2 diabetes in pregnancy was initially 2.38 per 1,000 pregnancies at the beginning of the study period. Between 1996 and 1999 the prevalence of type 2 diabetes in pregnancy fluctuated between 0.51 and 2.19 per 1,000 pregnancies. After 1999 the prevalence increased fairly steadily until 2003 from 1.36 to 3.78 per 1,000 pregnancies. There was a slight decrease in the prevalence of type 2 diabetes in pregnancy between 2003 and 2004, but it continued to increase after this from 3.08 per 1,000 in 2004 to 4.83 per 1,000 in 2008. After 2008 the prevalence of type 2 diabetes in pregnancy increased more rapidly from 6.71 to 10.37 per 1,000 pregnancies between 2009 and 2012 (Figure 6.1).

The sensitivity analysis showed that the estimated prevalence of pregestational diabetes mellitus in pregnancy does not change with increasing length of time a woman was registered with a practice prior to pregnancy for both type 1 and type 2 diabetes (Figure 6.2).

Figure 6.1: Scatter plot of the prevalence of pregestational diabetes mellitus in pregnancy by calendar year and diabetes type

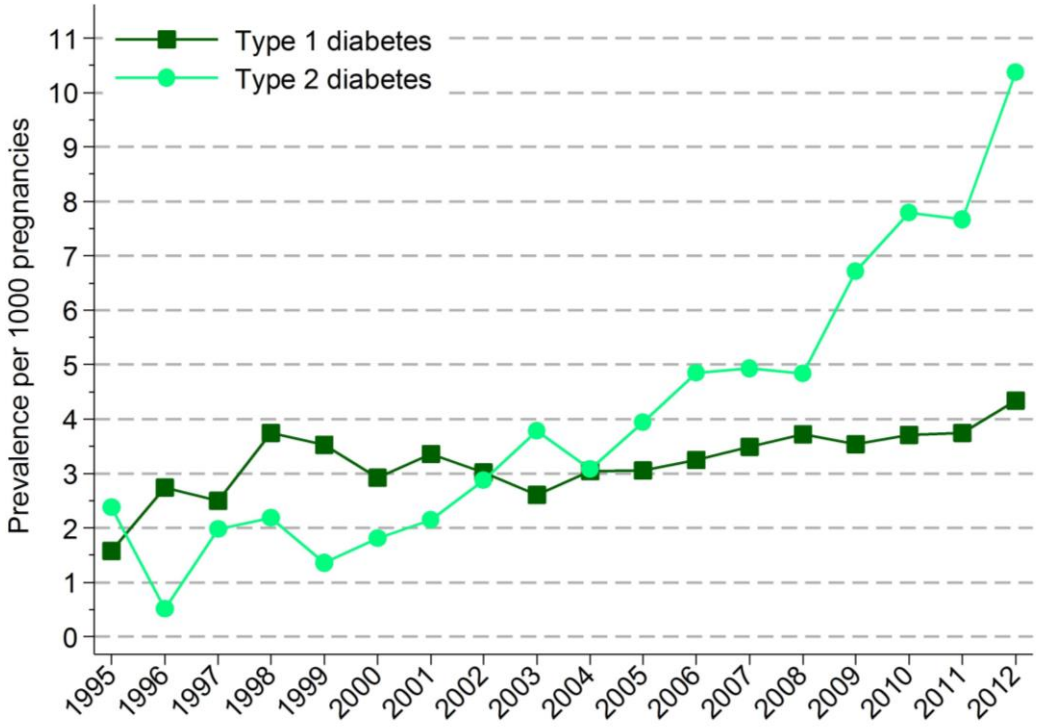
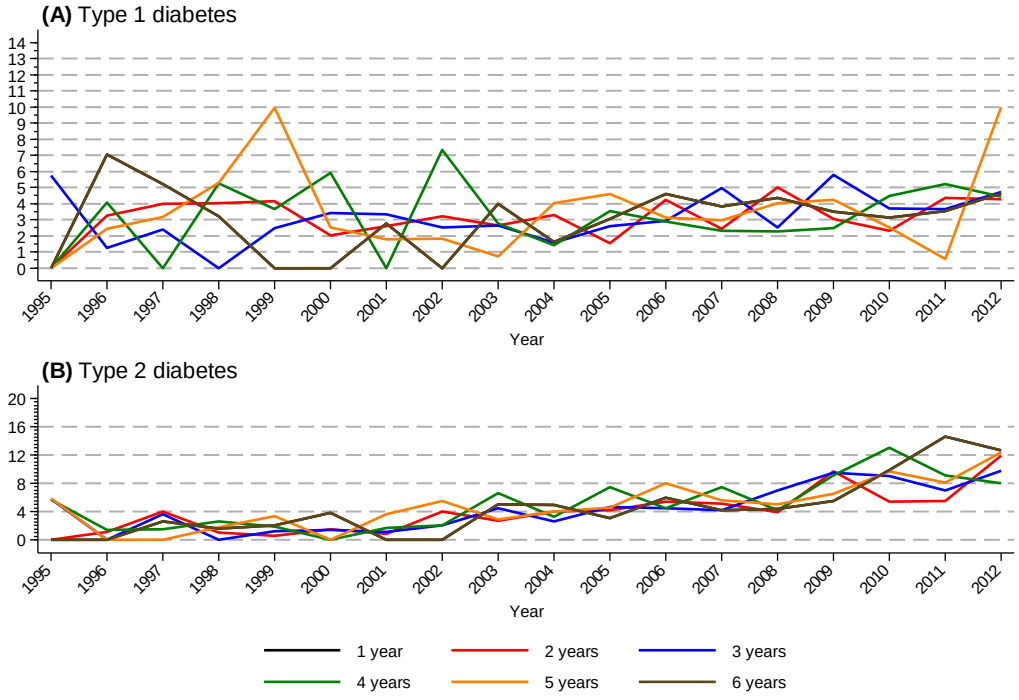
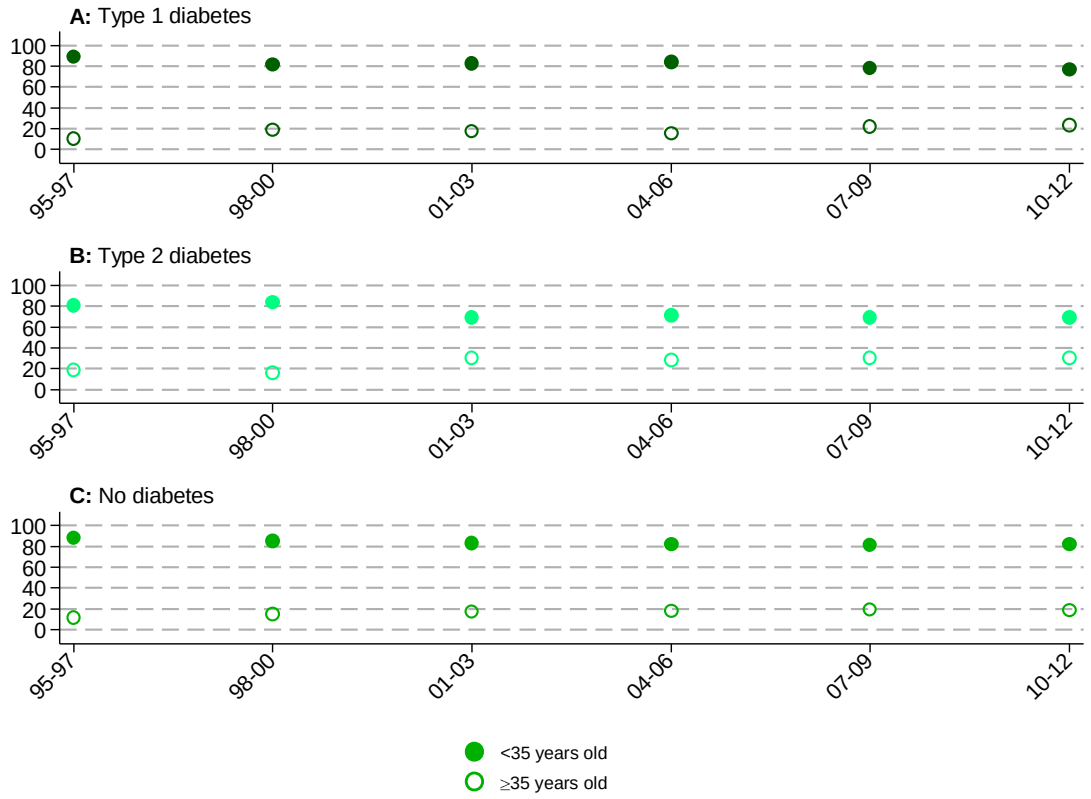


Figure 6.2: Sensitivity analysis of how the diagnosis, and as such the prevalence*, of pregestational diabetes in pregnancy is affected by length of time registered with a GP practice prior to pregnancy



*The prevalence of diabetes in pregnancy is calculated in a cohort restricted to patients registrated with a GP practice prior to pregnancy for at least 1-6 years respectively

Figure 6.3: Scatter plot of the temporal trends in the prevalence of maternal age at the start of pregnancy by calendar year period and diabetes status

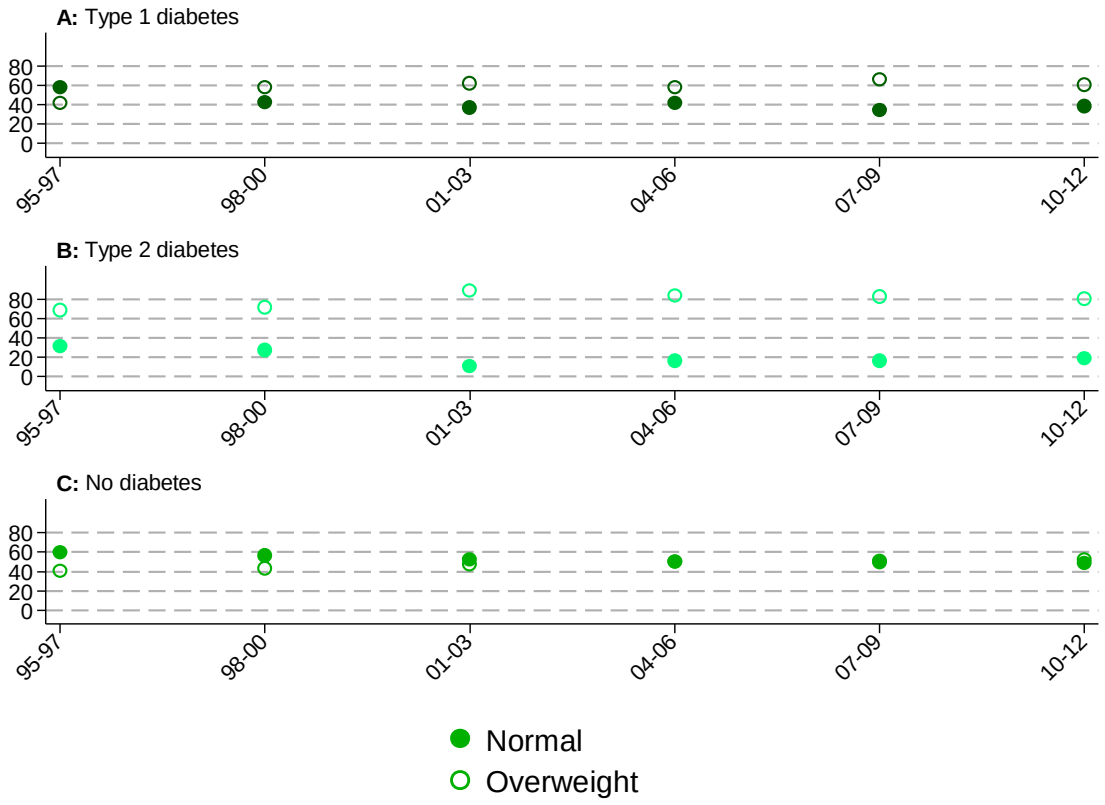


The temporal trends in the prevalence of maternal age at the start of pregnancy (categorised as under 35 years, or 35 years and older) for pregnant women with and without pregestational diabetes are illustrated in Figure 6.3. The prevalence of pregnant women aged 35 years or older at the start of the pregnancy increased over the study period for women with and without pregestational diabetes. For pregnant women without diabetes the prevalence of maternal age being 35 years and over at the start of pregnancy increased steadily over the study period from 12% in the calendar period 1995-97 to 18% in the calendar period 2010-12. The prevalence of pregnant women aged 35 years or older increased from 11% in 1995-97 to 23% in 2010-12 for pregnant women with type 1 diabetes. For women with pregestational type 2 diabetes the prevalence of women aged 35 years or older at the start of pregnancy was 19% in 1995-97 before dropping to 16% in the calendar period 1998-2000 and then remained between 29% and 31% until the end of the study period (Figure 6.3).

Finally, the temporal trends in the prevalence of maternal overweight prior to pregnancy for pregnant women with and without pregestational diabetes are illustrated in Figure 6.4. For pregnant women without pregestational diabetes the prevalence of overweight BMI

increased over the study period. In 1995-97 the prevalence was 40% increasing to 52% in 2010-12 for maternal overweight BMI (Figure 6.4). For pregnant women with pregestational type 1 diabetes the prevalence of maternal overweight BMI increased between the first and second time periods and then plateaued towards the end of the study period. In 1995-97 the prevalence of maternal overweight was 42% increasing to 58% in 1998-2000 before levelling off and remaining between 58% and 66% for the remainder of the study period. For pregnant women with pregestational type 2 diabetes the prevalence of overweight BMI increased from 69% in 1995-97 to 81% in 2010-12 (Figure 6.4).

Figure 6.4: Scatter plot of the temporal trends in the prevalence of maternal overweight at the start of pregnancy by calendar year period and diabetes status



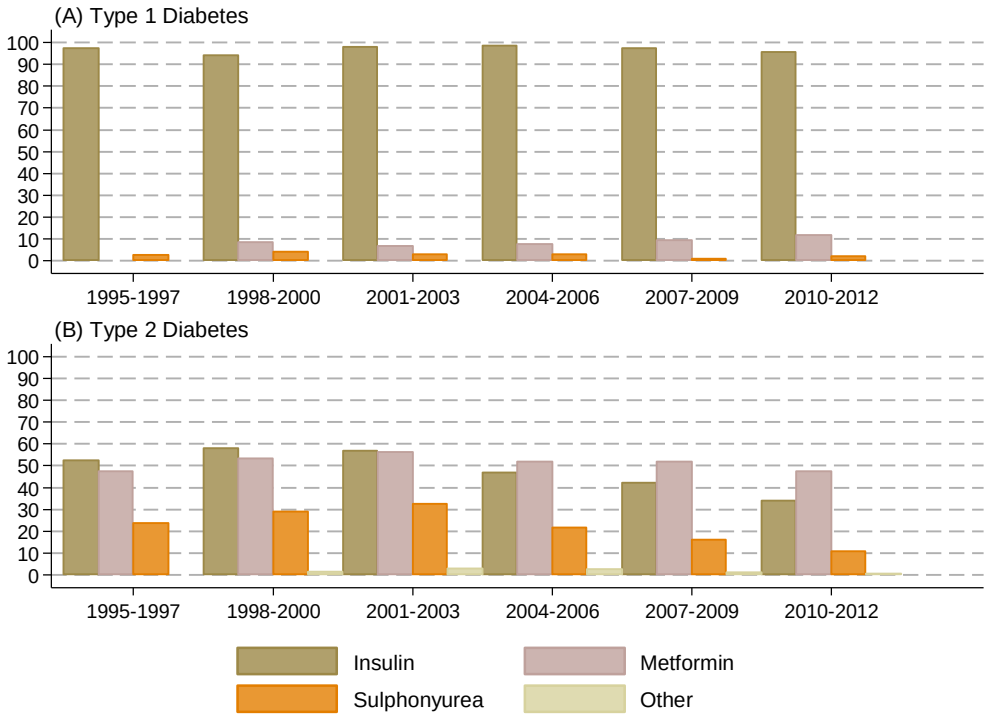
6.3.3 Objective three - Temporal trends in the prevalence of diabetic therapy prescriptions during pregnancy

In women with pregestational type 1 diabetes the prevalence of prescribing an antidiabetic therapy during pregnancy decreased between 1995 and 2012 for all therapy types, except metformin (Figure 6.5 (A)). The prevalence of women with type 1 diabetes being prescribed insulin during pregnancy decreased from 97% in the calendar period

1995-1997 to 96% in the calendar period 2010-2012, although there was no statistically significant difference (Table 6.4). The prevalence of prescribing of metformin in pregnant women with type 1 diabetes increased during pregnancy from 0% to 12% between calendar periods 1995-1997 and 2010-2012. After an initial increase from 3% to 4% between 1995-1997 and 1998-2000, the prevalence of prescribing sulphonylureas to women with type 1 diabetes decreased over the study period to 2% in 2010-2012.

The prevalence of prescribing during pregnancy to women with pregestational type 2 diabetes again decreased for all antidiabetic therapies (Figure 6.5 (B)). The prevalence of women with type 2 diabetes being prescribed insulin during pregnancy decreased from 52% to 34% between calendar periods 1995-1997 and 2010-2012. There was a (B)).

Figure 6.5: Bar graph of the prevalence of antidiabetic therapy prescribing by calendar year period and diabetes type



statistically significant difference in the prescribing of insulin to women with type 2 diabetes over the study period (Table 6.4). The prevalence of women with type 2 diabetes being prescribed sulphonylureas during pregnancy peaked at 33% in the calendar period 2001-2003 and then decreased to 11% by the end of the study period. Again, there was a significant difference in the prescribing of sulphonylureas to women with type 2 diabetes

Table 6.4: Univariate Poisson regression of each antidiabetic therapy category over calendar periods for women with type 1 and type 2 diabetes separately

Treatment	Year	Type 1 diabetes Rate ratio (95% CI)	p-value[1]	Type 2 diabetes Rate ratio (95% CI)	p-value[1]
Insulin	1995-1997	Ref	0.998	Ref	0.009
	1998-2000	0.967 (0.66, 1.41)		1.11 (0.56, 2.18)	
	2001-2003	1.00 (0.70, 1.44)		1.09 (0.58, 2.02)	
	2004-2006	1.01 (0.72, 1.43)		0.90 (0.49, 1.65)	
	2007-2009	1.00 (0.71, 1.41)		0.80 (0.44, 1.47)	
	2010-2012	0.98 (0.70, 1.38)		0.65 (0.36, 1.18)	
Metformin	1995-1997			Ref	0.001
	1998-2000			1.12 (0.55, 2.27)	
	2001-2003			1.18 (0.62, 2.26)	
	2004-2006			1.09 (0.58, 2.06)	
	2007-2009			1.09 (0.58, 2.05)	
	2010-2012			1.00 (0.53, 1.86)	
Sulphonylureas	1995-1997			Ref	0.03
	1998-2000			1.22 (0.45, 3.28)	
	2001-2003			1.36 (0.55, 3.39)	
	2004-2006			0.92 (0.37, 2.26)	
	2007-2009			0.68 (0.28, 1.69)	
	2010-2012			0.46 (0.19, 1.12)	

[1] P-value from F-statistic of Poisson model.

over the study period; p-value=0.03 (Table 6.4). Women with type 2 diabetes were less likely to be prescribed metformin during pregnancy at the end of the study compared to the beginning (p-value=0.001 (Table 6.4)). The prevalence of prescribing metformin started at 48% in the calendar period 1995-1997, peaked at 56% during the calendar period 2001-2003 before decreasing to 47% at the end of the study period 2010-2012 (Figure 6.5).

6.4 Discussion

6.4.1 Summary of results

Women with pregestational diabetes were: older, had higher BMI, were more likely to be overweight, and were registered with a general practice for longer prior to pregnancy when compared to pregnant women without pregestational diabetes. The mean age for women with type 1, type 2 and no diabetes was 29.5 years, 31.5 years, and 29.0 years respectively. The mean BMI for women with type 1, type 2, and no diabetes was

26.0kg/m^2, 31.0kg/m^2, and 25.1kg/m^2, respectively. Pregnant women with type 1 diabetes had poorer control of blood glucose concentrations, were more likely to have a blood glucose control test recorded prior to pregnancy and were more likely to have hyperglycaemia recorded in the 12 months prior to pregnancy then pregnant women with and without type 2 diabetes. Mean HbA_{1c} concentrations prior to pregnancy were 67.3mmol/mol for women with type 1 diabetes compared to 56.4mmol/mol for women with type 2 diabetes. Amongst those with hyperglycaemia in the 12 months prior to pregnancy 60% were type 1 diabetics and 34% were type 2 diabetics. Pregnant women with type 2 diabetes were more likely to be of non-white ethnicity when compared to women with type 1 diabetes.

The prevalence of type 1 diabetes in pregnancy increased between 1995 and 2012; it started at 1.58 per 1,000 pregnancies in 1995 and increased to 4.34 per 1,000 pregnancies in 2012. The prevalence of type 2 diabetes in pregnancy also increased between 1995 and 2012 but at a faster rate than the prevalence of type 1 diabetes and with a noticeable acceleration in the last 4 years of the study period; between 2008 and 2012. The prevalence of type 2 diabetes in pregnancy was 2.38 per 1,000 pregnancies at the beginning on the study period, increasing to 2.88 per 1,000 pregnancies in 2002. After this period, it rose steadily to 4.83 per 1,000 in 2008. After 2008 the prevalence of type 2 diabetes in pregnancy increased more rapidly to 10.37 per 1,000 pregnancies at the end of the study period.

For women with both type 1 and type 2 diabetes the prevalence of being prescribed an antidiabetic therapy decreased for all drug categories, except for metformin, over the study period. Insulin prescribing in women with type 1 diabetes decreased very slightly, with no statistically significant difference, from 97% in the calendar period 1995-1997 to 96% in the calendar period 2010-2012.

The prevalence of women with type 2 diabetes being prescribed insulin during pregnancy decreased, with a statistically significant difference, from 52% to 34% between calendar periods 1995-1997 and 2010-2012. Metformin prescribing in women with type 2 diabetes was as likely at the end of the study compared to the beginning of the study with the prevalence of prescribing metformin being 48% at the beginning and end of the study period.

6.4.2 Comparisons with current literature

There are few studies with the primary objective to investigate the prevalence of pregestational diabetes in pregnancy (34,76,79), of these studies only one is based in the UK (34). Bell *et al* (34) studied the trends in prevalence of pregestational diabetes in pregnancy in maternity units in the North of England between 1996 and 2004, and found comparable prevalence of type 1 diabetes but much lower prevalence of type 2 diabetes than our study. In 2002-04 they found a prevalence of 3.5 per 1,000 births of type 1 and 1.2 per 1,000 birth of type 2 diabetes. Of the non-UK based studies (76,79) López de Andrés *et al* (79) found in Spain that the prevalence of pregestational diabetes increased from 0.2% in 2001 to 0.27% in 2008. Lawrence *et al* (76) in the United States of America also found that the prevalence of pregestational diabetes more than doubled between 1999 and 2005 from 0.11% to 0.55% equivalent to my findings.

The Confidential Enquiry into Maternal and Child Health (CEMACH) in England, Wales and Northern Ireland reported prevalence of pregestational diabetes between 1 March 2002 and 28 February 2003 as part of a series of findings (78). They found a prevalence of type 1 and type 2 diabetes of 2.7 per 1,000 births and 1.0 per 1,000 births respectively. My findings are comparable to CEMACH for the prevalence of type 1 diabetes in pregnancy in 2002; 3.7 per 1,000 births, but higher for type 2 diabetes in pregnancy in 2002; 6.4 per 1,000 births. The CEMACH enquiry (78) found pregnant women with type 1 diabetes are different to pregnant women with type 2 diabetes in terms of age, ethnicity and parity. They found pregnant women with type 2 diabetes were older than women with type 1 diabetes; median age 33.5 years compared to 30.0 years respectively. These results compare favourably to the results from THIN presented in this chapter, where I found the mean age was 29.5 years for women with type 1 diabetes and 31.5 years for women with type 2 diabetes.

6.4.3 Strengths and limitations

THIN is a large primary care database capturing real life data from primary care and this was a significant strength of this study. However, THIN was not created for research purposes rather, it is clinical data entry system. Below I outline how this may have an impact on the recording of the data specific for this PhD project.

One of the limitations is that there is a large amount of missing data particularly for height, weight, BMI, and ethnicity. For BMI 10%, 11%, and 27% of women with type 1 diabetes,

type 2 diabetes, and without diabetes had no record, respectively. Whereas, for ethnicity approximately 35% of pregnant women have missing data across the three diabetes categories; 32%, 27%, and 35% for women with type 1 diabetes, type 2 diabetes, and without diabetes respectively. In this chapter I provided the information about the proportion of missing data for each variable and when I estimated the prevalence of e.g. smokers I took this into account. Had, I only considered the distribution among the individuals with records available I might have overestimated the proportion of smokers in the sample as these are more likely to have a record (80). In later chapters, I will be using this information for statistical modelling and the missing data may introduce bias to the results. To remove this bias, methods will be introduced to deal with the missing data, for example multiple imputation methods.

Another potential limitation of this study is that there may be an underestimation in the prevalence of diabetes. This may firstly be due to the algorithm used to identify pregnant women with diabetes. In this algorithm, I used diagnostic Read codes, prescriptions and free text entered by GPs to confirm diabetes and I excluded women with only one recording of diabetes and those receiving prescriptions for antidiabetics without a diagnostic code. For example, metformin is prescribed off license to women with polycystic ovary syndrome (PCOS) to help manage weight gain (14). However, by including women with prescriptions and no diagnostic codes I have may misclassified women with PCOS as having diabetes and artificially increased the prevalence of diabetes in pregnancy. On the other hand, pregnant women with pregestational diabetes could have been excluded. The algorithm used, also excluded women that had a first recording of diabetes during pregnancy. This may have led me to exclude some women with type 1 or type 2 diabetes first recognised in pregnancy.

A second factor that may have led to an underestimation in the prevalence of diabetes in pregnancy, stems from studies that have shown that as many as half those with type 2 diabetes remain undiagnosed. This is because their symptoms of hyperglycaemia sometimes go undetected and are not recorded in primary care (81). Therefore, my cohort may include some women that are classified as not having diabetes when in fact they do and it is just not diagnosed.

Thirdly, the algorithm used to identify and classify women as type 1 or type 2 diabetic was specific, I have chosen to have a specific rather than sensitivity approach to identifying women with pregestational diabetes in order to limit any false positive cases

of diabetes. In this chapter, this approach may have led to another source of underestimation of the prevalence of pregestational diabetes in pregnancy. In later chapters, where I examine adverse outcomes in pregnancy, this approach may again lead to a potential underestimation of the risk associated with having diabetes in pregnancy. But if I had chosen to identify women with pregestational diabetes using a sensitivity approach the effect of pregestational diabetes in pregnancy would have been diluted.

Another potential limitation of this study and THIN data in general was that information on important clinical characteristics surrounding pregnancy and birth was not recorded. I found that information on the maternal characteristics prior to pregnancy such as glycaemic control was not well recorded in THIN; HbA1c was not recorded in nearly half of women with type 1 diabetes in the year prior to pregnancy and nearly 70% of women with type 2 diabetes in pregnancy (see Table 6.2). Important delivery outcomes were also poorly recorded in primary care records; I investigated birthweight and five minute Apgar score but both were poorly recorded in the database. The information on the child at birth will be sent to the GP via the hospital discharge letter but would only be available to researchers if the information was subsequently coded into the primary care records. The practice of coding diagnostic information from discharge letters varies greatly by GP practice and is unlikely to be adequately recorded in the primary care records.

Lastly, THIN data is restricted to general practice attenders. Women with diabetes who receive their care privately or in specialist clinics would have been missed, contributing to under reporting of prevalence. Despite these considerations, the study reported higher than expected prevalence of diabetes than has previously been reported.

6.5 Conclusions

My findings show that in primary care the prevalence of pregestational diabetes in pregnancy has increased dramatically over the study period, from 1.58 to 4.34 per 1,000 pregnancies for women with type 1 diabetes and with type 2 diabetes increasing at a faster rate from 2.38 to 10.37 per 1,000 pregnancies. In addition they indicate that women with pregestational diabetes are: older, have a higher BMI, and blood pressure prior to pregnancy. They also indicate that women with type 1 diabetes have poorer control of their diabetes preceding pregnancy and that it is important for GPs to intensively monitor and support women with type 1 diabetes of child bearing age. Finally, my findings show

that prescribing antidiabetic treatments to women with type 1 and type 2 diabetes remains relatively unchanged over the study period, except for the decrease in prescribing of sulphonylureas.

The clinical implications related to these findings will be discussed in the final discussion chapter of the thesis.

6.6 Next chapter

In the next chapter I will be exploring the five outcomes of interest in more detail.

Chapter 7 Adverse maternal and child pregnancy outcomes

7.1 Introduction

The second study of my PhD focuses on the recording and the validity of the recording of the five selected outcomes of interest in UK primary care in comparison with the UK population. The outcomes of interest are preeclampsia, instrumental delivery, caesarean section delivery, perinatal death, and major congenital malformations.

In this chapter I will define each of the selected maternal and child adverse outcomes, followed by details of the medical record extraction process used for each outcome. I will then outline the statistical methods applied, before presenting the results. Finally, I will discuss the results in comparison with the existing literature, as well as evaluating the use of THIN in this context. The study specific objectives are outlined below in Section 7.3.1.

7.1.1 Study rationale

Women with diabetes are at an increased risk of experiencing adverse pregnancy outcomes when compared to women without diabetes in pregnancy. I have previously (Chapter 1, section 1.2.1) categorised adverse outcomes into two groups; complications of pregnancy due to diabetes and complications or worsening of diabetes due to pregnancy. This thesis focused on the first group of outcomes; complications of pregnancy due to diabetes, which can be further subdivided into: adverse outcomes for the mother and adverse outcomes for the child. I discovered from my broad literature review that a large proportion of the current literature focused on adverse outcomes for the child, mainly excluded women with type 2 diabetes in pregnancy, and when women with type 2 diabetes were included in the study sample analyses were not stratified by diabetes type. Therefore, I decided to select maternal outcomes to research for this thesis, included pregnant women with both type 1 and type 2 diabetes, and stratified my analysis by diabetes type.

Before I investigated whether women with diabetes in pregnancy have higher rates of adverse pregnancy outcomes I wanted to evaluate the recording of each outcome in

THIN. In the UK the majority of women give birth in secondary care, for example: delivery wards in hospitals, or at specialist mid-wife led units. Any adverse events will be recorded in secondary care at the time of the event and reported to the patients GP via the discharge letter or in consultation with the mother shortly after delivery. Due to this process there may be a chance that some events are not recorded in primary care and therefore do not appear in THIN. By comparing the prevalence of each outcome of interest as recorded in THIN to national figures I will be able to conduct an external validation of the recording of each outcome in THIN. In addition to having a potential effect on the prevalence of each outcome in primary care, there may be a time delay in the recording. Therefore, I expanded the recording period for each outcome on either side of the estimated delivery date to ensure I captured all recordings. The recording time periods for each outcome are detailed below.

7.2 Study cohort

The pregnancy cohort described in detail in Chapter 5, and used in the previous chapter, was used for this study. Briefly, the pregnancy cohort contains all women permanently registered with a THIN primary care practice, aged between 16 and 55 years old with an estimated delivery occurring between the 1st January 1995 and 31st December 2012.

In the following sections I describe how each of the outcomes of interest were defined and extracted from THIN primary care database.

7.2.1 Pregnancy outcome definitions

The five selected adverse maternal and child pregnancy outcomes were all defined using a similar process. Firstly, a code list for diagnostic Read and AHD codes related to each outcome was developed and reviewed by a clinician. For all of the selected outcomes the full list of Read and AHD codes used to identify relevant records are available in Appendix III. Secondly, all relevant health records were searched and records related to the outcomes, identified via the code list, were extracted. Depending on the outcome, the relevant health records would either be recorded using Read codes stored in the medical and the AHD records or recorded using AHD codes stored in the AHD records. Some of the selected outcomes could be recorded (using Read or AHD codes) in the child's health records as well as the mother's, in these cases both the mother's and the child's health records were searched.

The final step was to check the validity of the recording by ensuring the outcome had been recorded within a pre-specified time of the pregnancy. This final step will limit outcomes being mistakenly assigned to the wrong pregnancy, by keeping the recording limit within a reasonable time frame of the pregnancy occurring.

Whilst the process for defining the selected outcomes was similar, there were some differences for each outcome and these are described in detail below along with the outcome specific recording period.

7.2.1.1 Caesarean section delivery

Caesarean section is recorded using diagnostic Read codes and one AHD code related to delivery outcome (1055500000 – "CHS - delivery details"). It was not possible to distinguish between elective and emergency caesarean section, as such this outcome is a combination of all caesarean section deliveries. The mother and the child's medical and AHD records were searched and all related records extracted.

The recording period for caesarean section started four weeks prior to the estimated delivery date and ended at six months after the estimated delivery date for the mother's health records. The recording period extended from birth or registration with a THIN practice up to six months of age for the child's health records.

Any pregnant women that had a record related to caesarean section in the recording period, either within the mother's or child's health records, were defined as having had a caesarean section delivery.

7.2.1.2 Instrumental delivery

Instrumental delivery was defined as a composite maternal outcome of delivery assisted by ventouse or forceps. As such the list of diagnostic Read codes included all codes related to both ventuose and forceps delivery. In addition there was also one AHD code related to delivery outcome (1055500000, CHS - delivery details). The mother and the child's medical and AHD records were searched and all related records extracted.

The recording period for instrumental delivery started four weeks prior to the estimated delivery date and ended at six months after the estimated delivery date for the mother's health records. In the child's health records, the recording period for instrumental delivery extended from birth or registration with a THIN practice up to six months of age.

Any pregnant women that had a record related to instrumental delivery in the recording period, either within the mother's or child's health records, were defined as having had an instrumental delivery.

7.2.1.3 Preeclampsia

Clinically, pregnancy induced hypertension, or gestational hypertension, hypertension newly presenting after 20 weeks gestation. Were hypertension is defined: as systolic>140 mmHg or diastolic≥90 mmHg. Preeclampsia is characterised by: two hypertensive blood pressure measurements, and two high measures of protein in the urine; which is defined as a protein concentration>300mg/24 hours or protein:creatinine ratio of >30mg/mmol, both presenting at 20 weeks gestation or later (82). Eclampsia is a complication of preeclampsia, it occurs when the pregnant women experiences a fit or convulsion. The only way to cure preeclampsia and eclampsia is to deliver the baby.

Preeclampsia is a composite maternal outcome comprising of gestational hypertension, eclampsia, and preeclampsia; referred to from this point forward as preeclampsia. The recording period for preeclampsia began at 20 weeks gestation and extended to three months after the estimated delivery dates. Separate diagnostic Read code lists were developed for:

1. Eclampsia, preeclampsia or proteinuric hypertension of pregnancy;
2. Gestational hypertension;
3. And hypertension or hypertension monitoring.

The mother's medical and AHD records were searched using the three code lists and all related records were extracted. To be diagnosed as having preeclampsia, identified via diagnostic Read codes in one of the three lists, a woman had to have one record during the recording period.

In addition to this the mother's AHD records were searched for one AHD code related to blood pressure testing (1005010500 - "Blood pressure"). To be defined as having preeclampsia, identified via the AHD code for blood pressure (BP), a woman had to have at least two hypertensive blood pressure measurements during the recording period, with hypertension defined as systolic BP≥140mmHg and/or diastolic≥90mmHg.

7.2.1.4 Perinatal death

Perinatal death is defined as foetal deaths at 20 weeks gestation or later, and infant deaths that occur within the first seven days of life (83). A Read code list of diagnostic codes related to foetal death or loss, and infant or neonatal death was developed. The mother's medical and AHD records were searched and all related records extracted. The mother's AHD records were also searched for records of two AHD codes; 1015000000 – "Maternity outcome" and 1052500000 – "Maternity infant details".

In previous work it has been found that the rate of perinatal death recording within THIN is lower than in the UK population. Therefore, to identify all the women that had a record of perinatal death the free text records within the medical and AHD records were searched. This was achieved by applying to the data providers of THIN for a free text search for terms related to perinatal death. The free text search terms included still birth, foetal death, intrauterine death, neonatal death, infant death, and death of foetus, perinatal death, new born death, and all synonyms.

The recording period for perinatal death started at 20 weeks gestation and extended to seven days after the estimated delivery date. To be defined as having experienced perinatal death a woman had to have one relevant code or a free text record during the recording period.

7.2.1.5 Major congenital anomalies

Congenital anomalies, also known as birth defects, congenital disorders or congenital malformations, are developmental anomalies occurring during foetal life that can cause major structural abnormalities or functional deficits. They can be identified prenatally, at birth, or sometimes may remain unnoticed until later life (84). Major malformations can lead to severe physical disability or functional impairment requiring life-long medical treatment, care, surgery or death. Minor malformations are also structural abnormalities but they are minor and are less likely to affect one's life.

Major congenital anomaly was the only child outcome investigated in this PhD. A list of diagnostic Read codes was developed based on the EUROCAT guidelines (85). This list was then reviewed by a GP to ensure it only included codes for major anomalies and not minor anomalies. The mother and child's medical and AHD records were searched for relevant codes and all related records were extracted.

The recording period for major congenital anomaly started from the estimated start date of the pregnancy and extended up to six months after birth in the mother's health records. The recording period in the child's health records started from birth or registration with a THIN practice and extended up to the first year of life. If a child or linked mother had a diagnostic Read code for a major congenital anomaly, within the recording period that child was identified as having a major congenital anomaly.

7.3 Statistical methods

7.3.1 Study objectives

1. Calculate the prevalence of each outcome of interest in the pregnancy cohort.
2. Examine the temporal changes in the prevalence of each outcome of interest over the study period.
3. Examine the associations between maternal demographic and clinical characteristics with each outcome of interest.

7.3.2 Statistical methods

Objective 1 - Prevalence of each outcome of interest in the pregnancy cohort

The prevalence of each outcome was calculated using the pregnancy cohort. For each of the selected outcomes the denominator included all pregnancies with an estimated delivery date during the study period. The numerator included all pregnancies to all women that experienced the outcome. In this instance, as each outcome can only occur once during each pregnancy the prevalence is equivalent to incidence.

I conducted a sensitivity analysis where I varied the recording period for perinatal death to assess the effect on the prevalence. The initial recording period from 20 weeks gestation up to 1 week after birth was extended to: one month, two months and one year after birth, keeping the 20 weeks gestation as the starting point.

The prevalence of each outcome was also examined by pregnancy order. For each woman the pregnancy number was calculated so that her first pregnancy recorded in THIN was numbered one, her second pregnancy recorded in THIN was numbered two and so on, and then categorised into: first, second, third, and fourth or higher pregnancy. The prevalence of each outcome was calculated within each pregnancy order category, all pregnancies within the pregnancy cohort were included. It should be noted that as the

population within THIN is dynamic that the first pregnancy recorded in THIN may not be the woman's first pregnancy.

The timing of the first diagnostic recording of each outcome was also investigated. Recording could occur within seven time periods: the first trimester (estimated pregnancy start date until 14 weeks gestation); the second trimester (from 15 weeks gestation until 27 weeks gestation); the third trimester (from 28 weeks gestation until estimated delivery date); the six weeks after delivery; between six weeks and 12 weeks after delivery; between 12 weeks and six months after delivery; and more than six months after delivery. The prevalence of recording of each outcome was calculated within each of the seven time periods for the entire pregnancy cohort.

Objective 2 - Temporal trends in the prevalence of each outcome of interest

The temporal trends in the prevalence of each outcome were investigated by; calculating the prevalence of each outcome by calendar year, for the years 1995 to 2012 inclusive. For each year the denominator was all women that gave birth during that calendar year and the numerator was all women that had experienced the outcome during that calendar year.

Objective 3 - Associations between maternal characteristics and each outcome of interest

Summary statistics were calculated to examine the associations between maternal demographic and clinical characteristics and each outcome of interest in turn. The characteristics examined were: maternal age, pre-pregnancy BMI, Townsend deprivation score, ethnicity, smoking status, blood pressure, number of years registered with a THIN practice prior to pregnancy, alcohol dependence, and hyperglycaemia in the 12 months prior to pregnancy.

For continuous characteristics the mean and standard deviation were calculated, for categorical variables the total number and percent within each category were calculated for each outcome separately. Univariate Poisson regression was conducted for each outcome and maternal characteristic in turn.

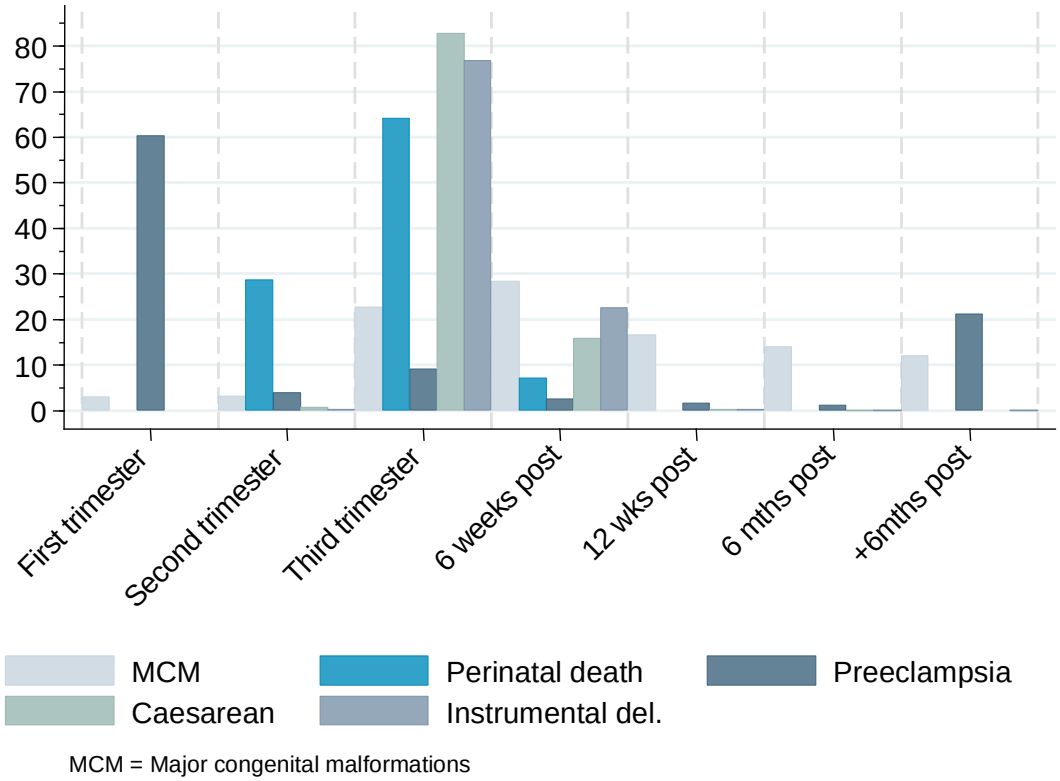
7.4 Results

7.4.1 Objective one - prevalence of each outcome in the pregnant population

The most common outcome of the five examined in this study was delivery by caesarean section. The prevalence of caesarean section delivery was 177.22 (95% CI (176.04, 178.40)) per 1,000 pregnancies. The next most common outcome was instrumental delivery; affecting 66.68 (95% CI (65.91, 67.45)) per 1,000 pregnancies in the pregnancy cohort. Major congenital malformations, perinatal death, and preeclampsia were the third, fourth, and least common outcomes respectively; affecting 15.68 (95% CI (15.30, 16.07)), 4.34 (95% CI (4.14, 4.55)), and 3.59 (95% CI (3.41, 3.78)) per 1,000 pregnancies in the pregnancy cohort (Table 7.1).

The sensitivity analysis into the recording period for perinatal death had little effect on the overall prevalence of perinatal death so the original time period of between 20 weeks gestation and one week after birth was retained.

Figure 7.1: Prevalence and timing of first recording of each adverse outcome across antenatal and postnatal periods



MCM = Major congenital malformations

Table 7.1: Number and prevalence of each outcome in the pregnancy cohort, N = 400,055

		N	Prevalence (95% CI) Per 1,000 pregnancies
Child outcomes			
	Major congenital malformations	6272	15.68 (15.30, 16.07)
Maternal outcomes			
	Perinatal death	1735	4.34 (4.14, 4.55)
	Preeclampsia[1]	1435	3.59 (3.41, 3.78)
	Caesarean section delivery	70896	177.22 (176.04, 178.40)
	Instrumental delivery	26674	66.68 (65.91, 67.45)

[1] Preeclampsia = Gestational hypertension, preeclampsia, and eclampsia

Table 7.2: Number and prevalence of each adverse outcome in the pregnancy cohort by pregnancy number

	Pregnancy number							
	First		Second		Third		Fourth or more	
	N	Prevalence per 1,000 (95% CI)	N	Prevalence per 1,000 (95% CI)	N	Prevalence per 1,000 (95% CI)	N	Prevalence per 1,000 (95% CI)
Child outcomes								
MCM[1]	4,597	15.25 (14.81, 15.69)	1,410	17.11 (16.24, 18.01)	217	16.09 (14.10, 18.36)	48	18.41 (13.90, 24.35)
Maternal outcomes								
Perinatal death	1,349	4.47 (4.24, 4.72)	321	3.89 (3.49, 4.34)	52	3.86 (2.94, 5.06)	14	5.37 (3.18, 9.05)
Preeclampsia[2]	1,315	4.36 (4.13, 4.60)	110	1.33 (1.11, 1.61)	9	0.67 (0.35, 1.28)	1	0.38 (0.05, 2.72)
Caesarean section	54,219	179.81 (178.44, 181.18)	14,059	170.56 (168.01, 173.14)	2,238	165.99 (159.80, 172.36)	380	145.76 (132.73, 159.84)
Instrumental delivery	24,146	80.08 (79.11, 81.05)	2,297	27.87 (26.76, 29.01)	200	14.83 (12.93, 17.02)	31	11.89 (8.37, 16.86)

[1] MCM = Major congenital malformations
[2] Preeclampsia = Gestational hypertension, preeclampsia and eclampsia

Table 7.3: Descriptive statistics and rate ratio for maternal demographic and clinical characteristics among women with caesarean section delivery

		Total cohort	Caesarean section			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value[1]
Age	years	400,055	70,896	30.2 (5.7)	1.0 (1.0, 1.0)	<0.001
Diastolic blood pressure	mmHg	278,820	48,292	73.8 (9.6)	1.0 (1.0, 1.0)	<0.001
Systolic blood pressure	mmHg	279,207	48,360	117.9 (13.4)	1.0 (1.0, 1.0)	<0.001
BMI[2]	kg/m^2	256,009	46,354	26.4 (5.7)	1.0 (1.0, 1.0)	<0.001
Prior registration[3]	years	400,055	70,896	7.9 (8.8)	1.0 (1.0, 1.0)	0.3
Age	16-24	95,338	11,916	12.5	1	<0.001
	25-34	233,994	42,035	18	1.4 (1.4, 1.5)	
	35-44	70,324	16,788	23.9	1.9 (1.9, 2.0)	
	45+	399	157	39.3	3.1 (2.7, 3.7)	
Smoking status	Never	168,211	30,422	18.1	1	<0.001
	Ex	122,497	22,637	18.5	1.0 (1.0, 1.0)	
	Current	106,258	17,413	16.4	0.9 (0.9, 0.9)	
	Missing	3,089	424	13.7		
Overweight	No	128,748	19,199	14.9	1	<0.001
	Yes	127,261	27,155	21.3	1.4 (1.4, 1.5)	
Alcohol dependence	No	398,253	70,597	17.7	1	<0.001
	Yes	1,802	299	16.6	0.9 (0.8, 1.0)	

		Total cohort	Caesarean section			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value[1]
Hyperglycaemia[4]	No	399,015	70,349	17.6	1	<0.001
	Yes	1,040	547	52.6	3.0 (2.7, 3.2)	
Townsend	1	88,076	16,306	18.5	1	<0.001
	2	74,946	13,603	18.2	1.0 (1.0, 1.0)	
	3	80,828	14,414	17.8	1.0 (0.9, 1.0)	
	4	78,198	13,334	17.1	0.9 (0.9, 0.9)	
	5	60,063	10,101	16.8	0.9 (0.9, 0.9)	
	Missing	17,944	3,138	17.5		
Ethnic group	White	180,016	32,441	18	1	<0.001
	Mixed	1,946	366	18.8	1.0 (0.9, 1.2)	
	Black	7,132	1,484	20.8	1.2 (1.1, 1.2)	
	Asian	14,216	2,744	19.3	1.1 (1.0, 1.1)	
	Other	4,846	937	19.3	1.1 (1.0, 1.1)	
	Missing	191,899	32,924	17.2		

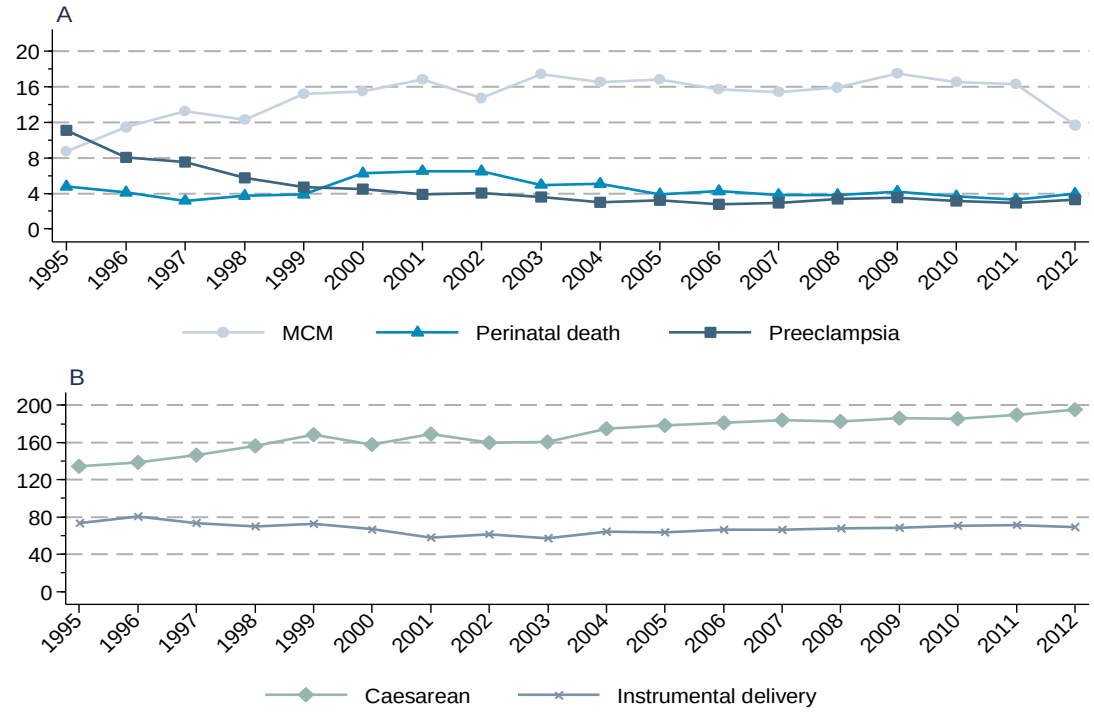
[1] P-value from Poisson model

[2] BMI- Body Mass Index

[3] Length of time registered with the GP prior to pregnancy

[4] Hyperglycaemia defined as HbA_{1c}>6.5% at the most recent test in the previous 12 months to pregnancy

Figure 7.2: Scatter plot of the temporal trends in the prevalence of each adverse pregnancy outcome



MCM = Major congenital malformations

The majority of women in the study cohort had a single pregnancy (75.4%) and only 0.7% of women had four or more pregnancies recorded in THIN. The prevalence of each outcome decreased with increasing pregnancy order, except for perinatal death and major congenital malformations (Table 7.2). The prevalence of perinatal death remained at approximately 4.0 per 1,000 pregnancies for all pregnancy order categories and the prevalence of major congenital malformations increased slightly from 15.25 (95% CI (14.81, 15.69)) per 1,000 pregnancies in the first recorded pregnancy to 18.41 (95% CI (13.90, 24.35)) per 1,000 pregnancies in the fourth or higher recorded pregnancy (Table 7.2).

The first record of caesarean section delivery, instrumental delivery, preeclampsia, and perinatal death were most frequent during pregnancy. Preeclampsia was most frequently recorded for the first time during the first trimester of pregnancy. Whereas, the two mode of delivery outcomes and perinatal death all had the highest prevalence of first recording during the third trimester of pregnancy. Major congenital malformation had the highest prevalence of first recording between delivery and six weeks post-delivery. Major congenital malformation and preeclampsia were the only outcomes to have a first recording in each of the seven time points (Figure 7.1).

7.4.2 Objective two - Temporal trends in the prevalence of outcomes

Over the study period; January 1995 to December 2012, perinatal death and preeclampsia were the least prevalent outcomes. There were very minor fluctuations in the prevalence of perinatal death between 3.2 and 6.5 per 1,000 pregnancies over the study period (Figure 7.2 (A)). Preeclampsia was the only outcome to decrease in prevalence over the study period. The prevalence of preeclampsia was 11.1 (95% CI (6.6, 18.6)) per 1,000 pregnancies in 1995 decreasing to 3.3 (95% CI (2.7, 4.0)) per 1,000 pregnancies in 2012 (Figure 7.2 (A)).The prevalence of major congenital malformation was initially 8.7 (95% CI (4.8, 15.7)) per 1,000 pregnancies in 1995 and then increased to approximately 15.1 (95% CI (13.1, 17.6)) per 1,000 pregnancies from 1999 until the end of the study period (Figure 7.2 (A)).

The two delivery outcomes; caesarean section and instrumental delivery, were the most prevalent outcomes across the study period. Caesarean section delivery was the most prevalent of the selected adverse outcomes in all calendar years and it increased in prevalence over the study period. Caesarean section increased from 134.6 (95% CI (116.9, 154.6)) per 1,000 pregnancies in 1995 to 195.3 (95% CI (191.0, 200.0)) per 1,000 pregnancies in 2012 (Figure 7.2 (B)). Instrumental delivery was the second most prevalent outcome for all calendar years during the study period. There were slight fluctuations in the prevalence of instrumental delivery, but overall the prevalence remained fairly consistent between 56.9 and 80.5 per 1,000 pregnancies (Figure 7.2 (B)).

7.4.3 Objective three - Associations between maternal characteristics and outcomes of interest

7.4.3.1 Caesarean section delivery

Women that had a caesarean section delivery were less likely to be smokers, they were more likely to have hyperglycaemia, lower Townsend deprivation score, or from an ethnic minority, and were older than women that don't deliver via caesarean section. There appeared to be a trend of increasing risk of caesarean section delivery as mothers got older. Thirteen percent of women that deliver via caesarean section were aged between 16 and 24 years old, compared to 18% aged 25-34 years old, 24% of women aged 35-44 years old, and nearly 40% of all women that deliver by caesarean section were aged

Table 7.4: Descriptive statistics and rate ratio for maternal demographic and clinical characteristics among women with instrumental delivery

		Total cohort	Instrumental delivery			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value[1]
Age	years	400,055	26,674	28.6 (5.7)	1.0 (1.0, 1.0)	<0.001
Diastolic blood pressure	mmHg	278,820	17,955	72.78 (9.2)	1. (1.0, 1.0)	0.2
Systolic blood pressure	mmHg	279,207	17,983	116.7 (12.8)	1.0 (1.0, 1.0)	0.2
BMI[2]	kg/m^2	256,009	17,044	24.3 (4.7)	1.0 (1.0, 1.0)	<0.001
Prior registration[3]	years	400,055	26,674	8.0 (8.9)	1.0 (1.0, 1.0)	0.05
Age	16-24	95,338	6,428	6.7	1	<0.001
	25-34	233,994	16,143	6.9	1.0 (1.0, 1.1)	
	35-44	70,324	4,092	5.8	0.9 (0.8, 0.9)	
	45+	399	11	2.8	0.4 (0.2, 0.7)	
Smoking status	Never	168,211	11,973	7.1	1	<0.001
	Ex	122,497	8,353	6.8	1.0 (0.9, 1.0)	
	Current	106,258	6,188	5.8	0.8 (0.8, 0.8)	
	Missing	3,089	160	5.2		
Overweight	No	128,748	9,751	7.6	1	<0.001
	Yes	127,261	7,293	5.7	0.8 (0.7, 0.8)	
Alcohol dependence	No	398,253	26,547	6.67	1	0.5
	Yes	1,802	127	7	1.1 (0.9, 1.3)	

		Total cohort	Instrumental delivery			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value[1]
Hyperglycaemia[4]	No	399,015	26,603	6.7	1	0.8
	Yes	1,040	71	6.8	1.0 (0.8, 1.3)	
Townsend	1	88,076	6,541	7.4	1	0.001
	2	74,946	5,449	7.3	1.0 (0.9, 1.0)	
	3	80,828	5,462	6.8	0.9 (0.9, 0.9)	
	4	78,198	4,708	6	0.8 (0.8, 0.8)	
	5	60,063	3,420	5.7	0.8 (0.7, 0.8)	
	Missing	17,944	1,094	6.1		
Ethnic group	White	180,016	13,355	7.4	1	0.002
	Mixed	1,946	124	6.4	0.9 (0.7, 1.0)	
	Black	7,132	219	3.1	0.4 (0.4, 0.5)	
	Asian	14,216	933	6.6	0.9 (0.8, 0.9)	
	Other	4,846	318	6.6	0.9 (0.8, 1.0)	
	Missing	191,899	11,725	6.1		

[1] P-value from Poisson model

[2] BMI- Body Mass Index

[3] Length of time registered with the GP prior to pregnancy

[4] Hyperglycaemia defined as HbA_{1c}>6.5% at the most recent test in the previous 12 months to pregnancy

Table 7.5: Descriptive statistics and rate ratio for maternal demographic and clinical characteristics among women with preeclampsia

		Total cohort	Preeclampsia*			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value
Age	years	400,055	1,435	28.4 (6.1)	1.0 (1.0, 1.0)	0.001
Diastolic blood pressure	mmHg	278,820	910	73.7 (8.4)	1.0 (1.0, 1.0)	0.001
Systolic blood pressure	mmHg	279,207	911	117.0 (11.1)	1.0 (1.0, 1.0)	0.3
BMI	kg/m^2	256,009	919	25.1 (4.9)	1.0 (1.0, 1.0)	0.7
Prior registration	years	400,055	1,435	7.0 (8.5)	1.0 (1.0, 1.0)	<0.001
Age	16-24	95,338	397	0.4	1	<0.001
	25-34	233,994	811	0.3	0.8 (0.7, 0.9)	
	35-44	70,324	222	0.3	0.8 (0.6, 0.9)	
	45+	399	5	1.3	3.0 (1.2, 7.3)	
Smoking status	Never	168,211	664	0.4	1	<0.001
	Ex	122,497	448	0.4	0.9 (0.8, 1.0)	
	Current	106,258	307	0.3	0.7 (0.6, 0.8)	
	Missing	3,089	16	0.5		
Overweight	No	128,748	444	0.3	1	0.2
	Yes	127,261	475	0.4	1.1 (1.0, 1.2)	
Alcohol dependence	No	398,253	1,427	0.4	1	0.6
	Yes	1,802	8	0.4	1.2 (0.6, 2.5)	

		Total cohort	Preeclampsia*			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value
Hyperglycaemia**	No	399,015	1,425	0.4	1	0.007
	Yes	1,040	10	1	2.7 (1.4, 5.0)	
Townsend	1	88,076	336	0.4	1	<0.001
	2	74,946	294	0.4	1.0 (0.9, 1.2)	
	3	80,828	288	0.4	0.9 (0.8, 1.1)	
	4	78,198	260	0.3	0.9 (0.7, 1.0)	
	5	60,063	200	0.3	0.9 (0.7, 1.0)	
	Missing	17,944	57	0.3		
Ethnic group	White	180,016	634	0.4	1	0.01
	Mixed	1,946	6	0.3	0.9 (0.4, 2.0)	
	Black	7,132	44	0.6	1.8 (1.3, 2.4)	
	Asian	14,216	55	0.4	1.1 (0.8, 1.4)	
	Other	4,846	12	0.3	0.7 (0.4, 1.2)	
	Missing	191,899	684	0.4		

* Preeclampsia = gestational diabetes, preeclampsia and eclampsia

** Hyperglycaemia in the 12 months prior to pregnancy

45 years or greater. In comparison to women that were aged 16-24 years of age women that were aged 45 years or greater at the start of pregnancy had three times the risk of having a caesarean section delivery; RR 3.1 (95% CI (2.7, 3.7)). Women that smoked at the start of pregnancy were 10% less likely to deliver via caesarean section than mothers that had never smoked at the start of pregnancy; RR 0.9 (95% CI (0.9, 0.9)). Women that were overweight at the start of pregnancy had nearly 1.5 times the risk of having a caesarean section delivery than women that were normal weight: RR 1.4 (95% CI (1.4, 1.5)). Over half of all women that had hyperglycaemia in the 12 months prior to pregnancy were delivered by caesarean section and had three times the risk of caesarean section when compared to women without hyperglycaemia in the 12 months prior to pregnancy: RR 3.0 (95% CI (2.7, 3.2)). Women in the two most socially deprived Townsend quintiles were 10% less likely to have a caesarean section delivery when compared to women in the least socially deprived Townsend quintiles: RR 0.9 (95% CI (0.9, 0.9)). Black women had 20% higher risk of caesarean section delivery when compared to white women; RR 1.2 (95% CI (1.1, 1.2)) (Table 7.3).

7.4.3.2 Instrumental delivery

Women that had an instrumental delivery were: younger, less likely to smoke, less likely to be socially deprived or from an ethnic minority then women that didn't have an assisted delivery. Women older than 35 years at the start of pregnancy were statistically less likely to have an instrumental delivery compared to women aged 16-24 years: RR 0.9 (95% CI (0.8, 0.9)) for women aged 35-44 and RR 0.4 (95% CI (0.2, 0.7)) for women aged 45 years or greater. Current smokers had 20% less risk of an instrumental delivery when compared to women that had never smoked at the start of pregnancy: RR 0.8 (95% CI (0.8, 0.8)). Women that were overweight at the start of pregnancy were 20% less likely to have an instrumental delivery when compared to women of normal BMI: RR 0.8 (95% CI (0.8, 0.8)). There appeared to be a trend of decreasing risk of instrumental delivery as social deprivation increased. Women in the two least socially deprived Townsend quintiles had the same risk: RR 1.0 (95% CI (0.9, 1.0)). Whereas, women in the middle and two most deprived quintiles had 10% and 20% reduction in risk of instrumental delivery when compared to women in the least socially deprived Townsend quintile. Women that are white were more likely to have an instrumental delivery when compared to black, Asian, mixed, and other ethnicities. Black women had the lowest risk of instrumental delivery when compared to white women: RR 0.4 (95% CI (0.4, 0.5)). Women that did and didn't experience an instrumental delivery appeared to be similar in

terms of; blood pressure, number of years registered with a THIN practice prior to pregnancy, history of alcohol dependence, and hyperglycaemia (Table 7.4).

7.4.3.3 Preeclampsia

Women with preeclampsia were older, more likely to never smoke, to have hyperglycaemia in the 12 months prior to pregnancy, less socially deprived, and more likely to be black when compared to pregnant women without preeclampsia. Pregnant women age 45 years old or greater were three times more likely to experience preeclampsia than women aged 16-24 years old at the at the start of pregnancy: RR 3.0 (95% CI (1.2, 7.3)). Women than smoked at the start of pregnancy were less likely to experience preeclampsia during pregnancy than women that had never smoked at the start of pregnancy: RR 0.7 (95% CI (0.6, 0.8)). Women with hyperglycaemia in the 12 months prior to pregnancy were nearly three times more likely to have preeclampsia than women without hyperglycaemia: RR 2.7 (95% CI (1.4, 5.0)). Women in the fourth and fifth Townsend quintiles for social deprivation were 10% less likely to have preeclampsia compared to women in the least deprived Townsend quintile: RR 0.9 (95% CI (0.7, 1.0)) for both quintiles. Black women were nearly twice as likely to have preeclampsia compared to white women: RR 1.8 (95% CI (1.3, 2.4)) (Table 7.5).

7.4.3.4 Perinatal death

Women that experience perinatal death were: older, overweight, more likely to smoke, have a history of alcohol dependence, hyperglycaemia in the prior 12 months, more socially deprived, and more likely to be from an ethnic minority when compared to women without perinatal death. Women aged between 35 and 45 years old were 30% more likely to experience perinatal death than women aged 16-24 years at the start of pregnancy: RR1.3 (95% CI (1.1, 1.5)). Perinatal death was 30% more likely among women that smoked at the start of pregnancy compared to women that never smoked: RR 1.3 (95% CI (1.1, 1.4)). Overweight women were 20% more likely to experience perinatal death when compared to women with normal BMI: RR 1.2 (95% CI (1.1, 3.0)). Women that had hyperglycaemia in the 12 months prior to pregnancy were over three times more likely to have a perinatal death than women without hyperglycaemia: RR 3.3 (95% CI (2.0, 5.6)). Women in the most socially deprived Townsend quintile had 60% higher risk of perinatal death than women in the least socially deprived quintile: RR 1.6 (95% CI (1.3, 1.8)). Black women were twice as likely to experience perinatal death and Asian women had 40%

Table 7.6: Descriptive statistics and rate ratio for maternal demographic and clinical characteristics among women with perinatal death

		Total cohort	Perinatal death			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value
Age	years	400,055	1,736	29.3 (6.3)	1.0 (1.0, 1.0)	0.01
Diastolic blood pressure	mmHg	278,820	1,350	73.7 (10.3)	1.0 (1.0, 1.0)	<0.001
Systolic blood pressure	mmHg	279,207	1,351	117.8 (14.0)	1.0 (1.0, 1.0)	0.001
BMI	kg/m^2	256,009	1,115	25.9 (5.8)	1.0 (1.0, 1.0)	<0.001
Prior registration	years	400,055	1,736	7.7 (8.6)	1.0 (1.0, 1.0)	0.4
Age	16-24	95,338	417	0.4	1	0.001
	25-34	233,994	925	0.4	0.9 (0.8, 1.0)	
	35-44	70,324	392	0.6	1.3 (1.1, 1.5)	
	45+	399	2	0.5	1.1 (0.3, 4.6)	
Smoking status	Never	168,211	702	0.4	1	0.001
	Ex	122,497	457	0.4	0.9 (0.8, 1.0)	
	Current	106,258	556	0.5	1.3 (1.1, 1.4)	
	Missing	3,089	21	0.7		
Overweight	No	128,748	519	0.4	1	0.01
	Yes	127,261	596	0.5	1.2 (1.0, 1.3)	

		Total cohort	Perinatal death			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value
Alcohol dependence	No	398,253	1,722	0.4	1	0.05
	Yes	1,802	14	0.8	1.8 (1.1, 3.0)	
Hyperglycaemia*	No	399,015	1,721	0.4	1	<0.001
	Yes	1,040	15	1.4	3.3 (2.0, 5.6)	
Townsend	1	88,076	329	0.4	1	0.002
	2	74,946	304	0.4	1.1 (0.9, 1.3)	
	3	80,828	329	0.4	1.1 (0.9, 1.3)	
	4	78,198	351	0.4	1.2 (1.0, 1.4)	
	5	60,063	348	0.6	1.6 (1.3, 1.8)	
	Missing	17,944	75	0.4		
Ethnic group	White	180,016	778	0.4	1	0.003
	Mixed	1,946	13	0.7	1.5 (0.9, 2.7)	
	Black	7,132	62	0.9	2.0 (1.6, 2.6)	
	Asian	14,216	89	0.6	1.4 (1.2, 1.8)	
	Other	4,846	19	0.4	0.9 (0.6, 1.4)	
	Missing	191,899	775	0.4		

* Hyperglycaemia in the 12 months prior to pregnancy

Table 7.7: Descriptive statistics and rate ratio for maternal demographic and clinical characteristics among women with major congenital malformations

		Total cohort	Major congenital malformations			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value
Age	years	400,055	6,272	29.1 (6.0)	1.0 (1.0, 1.0)	0.02
Diastolic blood pressure	mmHg	278,820	4,342	73.0 (9.4)	1.0, 1.0, 1.0)	0.04
Systolic blood pressure	mmHg	279,207	4,350	116.9 (13.3)	1.0, 1.0, 1.0)	0.1
BMI	kg/m^2	256,009	4,010	25.4 (5.4)	1.0 (1.0, 1.0)	0.06
Prior registration	years	400,055	6,272	8.9 (9.0)	1.0 (1.0, 1.0)	<0.001
Age	16-24	95,338	1,512	1.6	1	<0.001
	25-34	233,994	3,544	1.5	1.0 (0.9, 1.0)	
	35-44	70,324	1,205	1.7	1.1 (1.0, 1.2)	
	45+	399	11	2.8	1.7 (1.0, 3.1)	
Smoking status	Never	168,211	2,541	1.5	1	<0.001
	Ex	122,497	1,962	1.6	1.1 (1.0, 1.1)	
	Current	106,258	1,733	1.6	1.1 (1.0, 1.1)	
	Missing	3,089	36	1.2		
Overweight	No	128,748	1,721	0.4	1	0.05
	Yes	127,261	15	0.2	1.1 (1.0, 1.1)	
Alcohol dependence	No	398,253	6,234	1.6	1	<0.001
	Yes	1,802	38	2.1	1.4 (1.0, 1.9)	

		Total cohort	Major congenital malformations			
		N	N	Mean (SD) or %	Rate ratio (95% CI)	p-value
Hyperglycaemia*	No	399,015	6,219	1.6	1	<0.001
	Yes	1,040	53	5.1	3.3 (2.5, 4.3)	
Townsend	1	88,076	1,357	1.5	1	0.4
	2	74,946	1,146	1.5	1.0 (0.9, 1.1)	
	3	80,828	1,310	1.6	1.1 (1.0, 1.1)	
	4	78,198	1,264	1.6	1.0 (1.0, 1.1)	
	5	60,063	960	1.6	1.0 (1.0, 1.1)	
	Missing	17,944	235	1.3		
Ethnic group	White	180,016	2,907	1.6	1	0.1
	Mixed	1,946	24	1.2	0.8 (0.5, 1.1)	
	Black	7,132	103	1.4	0.9 (0.7, 1.1)	
	Asian	14,216	211	1.5	0.9 (0.8, 1.1)	
	Other	4,846	62	1.3	0.8 (0.6, 1.0)	
	Missing	191,899	2,965	1.5		

* Hyperglycaemia in the 12 months prior to pregnancy

higher risk of perinatal death when compared to white women: RR 2.0 (95% CI (1.6, 2.6)) for black women and RR 1.4 (95% CI (1.2, 1.8)) for Asian women (Table 7.6).

7.4.3.5 Major congenital malformations

Women that deliver a baby with a major congenital malformation were: older, more likely to have hyperglycaemia, more likely to have a history of alcohol dependence, and more likely to be white. Women aged 45 years and over have a 70% increased risk of major congenital malformations compared to women aged 16-24 years old: RR 1.7 (95% CI (1.0, 3.1)). Women that smoked or had formerly smoked prior to pregnancy had a 10% increased risk of major congenital malformations compared to women that had never smoked prior to pregnancy: RR 1.1 (95% CI (1.0, 1.1)) for both former and current smokers. In comparison to women that did not have a history of alcohol dependence prior to pregnancy, women that did have a history were 40% more likely to deliver a baby with major congenital malformation: RR 1.4 (95% CI (1.0, 1.9)). Women with hyperglycaemia in the 12 months prior to pregnancy were over three times more likely to have a baby with a major congenital malformation compared to women without hyperglycaemia: RR 3.3 (95% CI (2.5, 4.3)) (Table 7.7).

7.5 Discussion

7.5.1 Summary of results

Of the five selected outcomes the two delivery outcomes; caesarean section and instrumental delivery, were the most common. Caesarean section delivery affected 177.22 (95% CI (176.04, 178.40)) per 1,000 pregnancy, and instrumental delivery affected 66.68 (95% CI (65.91, 67.45)) per 1,000 pregnancies. Major congenital malformations affected 15.68 (95% CI (15.30, 16.07)) per 1,000 pregnancies and perinatal death and preeclampsia affected 4.34 (95% C I (4.14, 4.55)) and 3.59 (95% CI (3.41, 3.78)) per 1,000 pregnancies, respectively.

7.5.2 Comparison with current literature

The prevalence of congenital malformations, and perinatal mortality recorded in THIN is comparable to national figures. The British and Irish Network of Congenital Anomaly Researchers (BINOCAR) use six regional disease-specific registers collectively covering 36% of England, Wales, Scotland, and Ireland. In 2012 BINOCAR found 184 per 10,000

total births were affected by major congenital anomalies, slightly higher than the prevalence found in THIN of, 156.8 per 10,000 pregnancies (86). The European surveillance of major congenital anomalies (EUROCAT) found a slightly lower birth prevalence of major congenital anomalies in 2012 than BINOCAR, 177 per 10,000 but again, it was slightly higher than the prevalence found in THIN (87).

The Confidential Enquiry into Maternal and Child Health (CEMACH) report from 2009 found a birth prevalence of 7.6 (95% CI (7.4, 7.8)) per 1,000 births for perinatal mortality compared to 4.34 (95% CI (4.14, 4.55)) per 1,000 pregnancies recorded in THIN (88). The Maternal, Newborn, and Infant Clinical Outcome Review Programme, delivered by Mothers and Babies: Reducing Risk through Audits and Confidential Enquires across the UK (MBRRACE-UK), found a birth prevalence of 5.50 (95% CI (5.34, 5.67)) per 1,000 births for perinatal mortality in 2013 (89). MBRRACE-UK perinatal mortality prevalence findings are comparable to what I found in THIN, but the CEMACH findings indicate a higher prevalence of perinatal mortality.

The last national eclampsia incidence audit was conducted in 1992 by Douglas *et al* (90). The audit found nearly one in every 2,000 maternities (a pregnancy that resulted in a live or still birth) was affected by eclampsia: 4.9 per 10,000 maternities (90). The results from a five year prospective study of maternity units in Yorkshire between 1999 and 2003, found the prevalence of eclampsia to be 3.89 per 10,000 deliveries (91). These findings are comparable to the Douglas *et al* findings and my findings in THIN. In 2000 the WHO published regional incidence rates for preeclampsia and eclampsia (92). The WHO sub-region that includes the UK is, Euro A, and the incidence of preeclampsia and eclampsia in this sub-region was 0.4% and 0.8% respectively. The overall figure for preeclampsia in THIN was 3.59 (95% CI (3.41, 3.78)) per 1,000 pregnancies.

Caesarean section was the only outcome to increase in prevalence substantially over the study period, increasing from 134.6 (95% CI (116.9, 154.6)) per 1,000 pregnancies in 1995 to 195.3 (95% CI (191.0, 200.0)) per 1,000 pregnancies in 2012. The prevalence of major congenital malformations increased slightly from 8.7 (95% CI (4.8, 15.7)) per 1,000 pregnancies to 11.7 (95% CI (10.5, 12.9)) per 1,000 pregnancies. Preeclampsia was the only outcome to decrease in prevalence substantially over the study period, decreasing from 11.1 (95% CI (6.6, 18.6)) per 1,000 pregnancies in 1995 to 3.3 (95% CI (2.7, 4.0)) per 1,000 pregnancies in 2012. The prevalence of instrumental delivery and perinatal

death fluctuated between: 61.3 and 80.5 per 1,000 pregnancies; and 3.3 and 6.5 per 1,000 pregnancies, respectively.

The Health & Social Care Information Centre (HSCIC) published NHS maternity statistics between April 2012 and March 2013 from hospital episodes statistics data for England and found the 25.5% of deliveries are by caesarean section and 12.8% of deliveries are instrumental (93). The prevalence for both caesarean section and instrumental delivery was lower in THIN when compared to the HSCIC figures: 17.5% of deliveries were by caesarean section and 7.2% were instrumental in THIN.

7.6 Next chapter

The five outcomes of interest: caesarean section, instrumental delivery, preeclampsia, perinatal death, and major congenital malformations are well recorded in THIN. Although, the recorded prevalence of caesarean section, instrumental delivery, and perinatal death were lower in THIN compared to the literature.

In the next chapter I will examine whether women with pregestational diabetes in THIN have a greater risk of the selected adverse outcomes.

Chapter 8 The risk of adverse maternal and child pregnancy outcomes due to pregestational diabetes in pregnancy

8.1 Introduction

In this chapter I will build on previous work presented in this thesis. In the first study (Chapter 6) I found that over the study period, there was a significant increase in the prevalence of type 1 and type 2 diabetes in pregnancy. In the second study of this thesis (Chapter 7) I found that the prevalence of adverse maternal and foetal outcomes in pregnancy recorded in THIN ranged from 3.60 per 1,000 pregnancies for preeclampsia up to 177.19 per 1,000 pregnancies for caesarean section and were comparable to national average figures reported in the literature. The main aim for this chapter was to calculate the risk of each adverse maternal and foetal pregnancy outcome for women with type 1 or type 2 diabetes in pregnancy compared to women without diabetes in pregnancy, affectively bringing the first and second studies together.

8.2 Background

I previously reported that women with diabetes during pregnancy are at an increased risk of experiencing adverse pregnancy outcomes when compared to women without diabetes in pregnancy. For example, women with diabetes during pregnancy are at an increased risk of spontaneous abortion, caesarean section, perinatal mortality, and major congenital malformations (29,34,45,53,55).

The increased risk of adverse outcomes in pregnancy for women with pregestational diabetes is well established. In 1989 representatives from European governments, including the United Kingdom, met and agreed upon a number of five-year recommendations, to prevent diabetes and reduce complications from diabetes. The recommendations are referred to as the St Vincent declaration. The main aim of the declaration was to improve the health of people with diabetes so as to make their health comparable to that of a non-diabetic person, and specifically to improve the outcomes for

pregnant women with diabetes. So the risks of adverse outcomes for women with diabetes in pregnancy are equivalent to pregnant women without diabetes (37).

Since the St Vincent declaration there have been a number of studies that have investigated the reduction of adverse pregnancy outcomes in women with diabetes (42,43) and they found that adverse pregnancy outcomes in women with type 1 diabetes remained substantially higher decades after the St Vincent declaration. In women with type 1 diabetes, 10 years after the St Vincent declaration, Platt *et al* (43) reported the prevalence of congenital malformations to be 90.3 (95% CI (65.9, 120.1)) per 1,000 compared to national figures of 8.5 per 1,000 and the prevalence of perinatal mortality to be 43.0 (95% CI (26.5, 65.6)) per 1,000 compared to 8.4 per 1,000 in national figures. The study only included 547 women with type 1 diabetes attending one of 10 maternity units in the North of England between 1995 and 1999 and compared national rates from the Office for National Statistics (ONS). Colstrup *et al* (42) reported the risk of the adverse outcomes: congenital malformations, perinatal mortality, preterm delivery, and large for gestational age, were two to five times higher in women with type 1 diabetes than the general population. These studies focused on the effects of type 1 diabetes on pregnancy and were conducted in hospital based populations. The estimates from Platt and Colstrup were potentially on the higher end of the scale as women with type 1 diabetes usually have longer disease duration than women with type 2 diabetes prior to pregnancy and they also have more chaotic glycaemic control. The study described in this chapter however, investigates both type 1 and type 2 diabetes in pregnancy using primary care data.

The main aim for this study was to calculate the risk of each adverse maternal and foetal pregnancy outcome for women with type 1 or type 2 diabetes in pregnancy compared to women without diabetes in pregnancy. Using The Health Improvement Network (THIN) primary care database I was able to study whether women with pregestational type 1 and type 2 diabetes in pregnancy were at an increased risk of specific adverse pregnancy outcomes. THIN data is longitudinal in nature so I was able to investigate whether the risk of adverse pregnancy outcomes for women with diabetes altered over time and I was able to assess to what extent this risk compares to women without diabetes in pregnancy.

8.2.1 Study objectives

The key objectives were to:

1. Calculate the absolute risk and risk difference of each of the selected adverse pregnancy outcomes for women with type 1 diabetes, type 2 diabetes, and without diabetes in pregnancy.

2. Calculate temporal trends in the absolute risk of each of the selected adverse outcomes adjusting for differences in demographic and clinical characteristics in women with and without pregestational diabetes in pregnancy.

3. Estimate the relative risk of each of the selected adverse pregnancy outcomes adjusting for differences in demographic and clinical characteristics in women with and without pregestational diabetes in pregnancy.

8.3 Methods

This study was a retrospective cohort. The pregnancy cohort developed previously in the thesis and used in the first and second studies was used again for this study. The development of the pregnancy cohort was described in detail in Chapter 5. Briefly, the pregnancy cohort contains all pregnant women delivering between the 1st January 1995 and 31st December 2012, aged between 16 years and 55 years old, and permanently registered with a practice contributing data to THIN.

The process of identifying women with diabetes and classifying as either type 1 or type 2 diabetic was described in detail in Section 5.2.3.3. Briefly, diabetes was identified via records of diagnosis, prescriptions, and diabetes monitoring. Diabetes status was classified by considering diagnosis type, prescriptions, whether the diagnosis was incident, and age at diagnosis. Maternal demographic and clinical characteristic definitions and the process for extracting the variables were also described in detail in Chapter 5. The process of extracting and defining caesarean section delivery, instrumental delivery, preeclampsia, perinatal death, and major congenital malformations was described in detail in the previous chapter (Chapter 7).

8.3.1 Statistical methods

Objective one – Estimate absolute and relative risks

The absolute risk and 95% CI of each outcome was calculated in women with type 1 diabetes, type 2 diabetes, and women without diabetes. For each outcome the numerator was the number of women that experienced the outcome and the denominator was the number of women in each of the three groups. The risk difference and 95% CI for each

outcome was calculated, comparing the risk of the outcomes in women with type 1 diabetes to women without diabetes and comparing the risk in women with type 2 diabetes to women without diabetes. These calculations were performed for the whole cohort with a single randomly selected pregnancy per women.

Objective two – Temporal trends

To investigate the temporal trends in the risk of each outcome the risk of each outcome was calculated by diabetes status: women with type 1 diabetes, type 2 diabetes, and women without diabetes in pregnancy, and by calendar year period during the study period. Due to there being small numbers of observed outcomes for some of the outcomes, I combined the calendar years into calendar periods: 2000-2002, 2003-2005, 2006-2008, and 2009-2012. The cohort of a single randomly selected pregnancy per women was used for these calculations on the combined time points.

Objective three – Unadjusted and adjusted risk ratios

Poisson regression was used to estimate the risk ratio of each outcome adjusted for the specific demographic and clinical characteristics listed below. Comparisons were made between women with type 1 diabetes and women with type 2 diabetes to women without diabetes.

The potential maternal demographic and clinical characteristics included in the adjusted Poisson regression model were: age at the start of pregnancy, blood pressure prior to pregnancy, Townsend quintile (a measure of social deprivation), smoking status prior to pregnancy, a history of alcohol dependence prior to pregnancy, an indicator for hyperglycaemia in the 12 months prior to pregnancy, and an indicator for overweight prior to pregnancy.

The process of generating an adjusted Poisson regression model was conducted independently for each outcome but followed the same rules. The first phase of the model building was to identify which maternal characteristics were potential confounders, this was a two-step process. To begin with I examined if each of the maternal characteristics were associated with diabetes by applying a univariate regression analysis with diabetes status as the ‘outcome’ and each maternal characteristic in turn as a single predictor. I deemed characteristics to be significantly associated with diabetes status if the p-value <0.1. The second step was to examine which of the maternal characteristics were

associated with the outcomes. This was done by conducting a univariate regression analysis with each adverse pregnancy outcome as the outcome in turn and each maternal characteristic as a single predictor. As before all maternal characteristics associated with each adverse pregnancy outcome, p-value<0.1, were deemed to be significantly associated. For a maternal characteristic to be considered as a potential confounder it had to be associated with both diabetes status and the adverse pregnancy outcome in the univariate analysis and not on the causal pathway.

The second phase of the model building process involved generating the final model and conducting a complete case analysis for each adverse outcome. For each adverse outcome a complete case identifier was generated, so that only women with completely observed information for the adverse outcome, diabetes status and the set of confounders identified from the univariate analysis were included. The adjusted Poisson model was then conducted on this set of women; confounders were added one at a time in the order outlined in Table 8.1 until all identified confounders had been added to the model.

Table 8.1: The order that confounders were added to the adjusted Poisson regression model

Model name	**Maternal characteristics included in the model**
Univariate	Adverse outcome = Diabetes
Bivariate	Univariate + Maternal age
Clinical	Bivariate + Blood pressure prior to pregnancy Overweight prior to pregnancy Hyperglycaemia in the previous year
Behavioural	Clinical + Smoking status prior to pregnancy History of alcohol dependence
Deprivation	Behaviour + Townsend quintile for deprivation

The final phase of the model building was to conduct a cohort analysis using multiple imputation techniques to impute the missing data. The multiple imputation techniques are described in more detail below (Section 8.3.1.2).

8.3.1.1 Multiple Imputation

Missing or unobserved data occur in almost all epidemiological and clinical studies. In THIN, data can be missing for a number of reasons; the individual did not attend their appointment, the clinician did not ask the patient or they asked and did not record it, or more specifically the scales were broken on the day of the individual appointment so they were unable to be weighed.

There are a number of ways to handle missing data. The most commonly applied technique is complete case analysis. This is when only individuals with completely observed data for all variables required for the analysis are included. If there are a lot of variables with missing data or one variable with a large amount of missing data required in the analysis then a large proportion of the sample can be excluded; resulting in a loss of power and precision. Complete case analysis could also lead to bias if for example particular groups have more missing data than others. There are other ad-hoc methods for dealing with missing data, these methods can also lead to bias as the single imputation does not account for the uncertainty around the missing value leading to standard errors being smaller than they should be (94).

Multiple imputation accounts for the uncertainty around the missing value by creating several imputed datasets and the results from each dataset are then combined. Multiple imputation is a two-step procedure. Firstly, multiple copies of the dataset are created with missing values imputed in each dataset. The second step is to conduct the statistical analysis on each imputed dataset in turn and combine the results using Rubin's rule (95).

8.3.1.2 Methods of multiple imputation used in this study

In this study there were large amounts of missing data. For the whole pregnancy cohort 50% of women did not have a recording of ethnicity, approximately 30% of women that did not have a recording of blood pressure or BMI in the 12 months prior to pregnancy, 4% did not have a recording of Townsend deprivation score, and under 1% had a missing smoking status. If I were to conduct an analysis based on complete cases including all of the above variables my sample size would reduce from 399,993 pregnancies to just

104,145 pregnancies; only 26% of the pregnancy cohort had complete data. I therefore wanted to apply multiple imputation to improve the precision of my analysis and reduce potential bias introduced via complete case analysis.

To impute the missing values in the pregnancy cohort data I used the *mi impute suite* of commands available within Stata. I used the chain equation command, with the truncated regression option, and imputed 10 cycles of data to impute systolic blood pressure, diastolic blood pressure, BMI, ethnicity, smoking status, Townsend deprivation score. The full imputation model included all variables with missing data, an indicator of each of the five outcome variables (caesarean section, instrumental delivery, perinatal death, preeclampsia, and major congenital malformations), diabetes status, age, pregnancy number recorded in THIN, alcohol dependence, and hyperglycaemia in the year prior to pregnancy.

The basic idea with chain equation imputation is that each variable with missing data is modelled separately using all other variables (fully and partially observed) in the equation. In the first cycle of chain equations missing values are imputed using a random generator and values are imputed based on these. In the second cycle of the chain equations the missing values are imputed using the imputed values from the first cycle. Using the newest values to impute the next cycle of the chain equation continues until the full number of cycles has been imputed.

The models developed in the complete case analysis for each outcome for objective four of the study were then applied to the datasets imputed using chain equations.

8.4 Results

The pregnancy cohort of women delivering between 1st January 1995 and 31st December 2012 contained 400,055 pregnancies from 301,536 women. The proportion of pregnancies affected by pregestational diabetes was 0.8% (3,377) in the entire pregnancy cohort and 2,566 (0.9%) after randomly selecting one pregnancy per women.

8.4.1 Objective one - The absolute risk and risk difference of adverse outcomes by diabetes status

The absolute risk for each adverse outcome was higher in women with pregestational diabetes when compared to women without diabetes in pregnancy, except for

instrumental delivery. Of the adverse outcomes studied, women were at greatest absolute risk of being delivered by a caesarean section, followed by: an instrumental delivery, major congenital malformations, perinatal death, and preeclampsia had the lowest risk (Figure 8.1).

Women with type 1 diabetes in pregnancy were at higher absolute risk of experiencing a caesarean section delivery, preeclampsia, and major congenital malformations (MCM) compared to women with type 2 diabetes and without diabetes in pregnancy (Figure 8.1 (A) and (B)). Women with type 1 diabetes had an absolute risk of caesarean section that was three times higher than women without diabetes during pregnancy, and 1.5 times higher than women with type 2 diabetes in pregnancy. The absolute risk of caesarean section for: women with type 1 diabetes was 510.1 (95% CI (483.7, 547.5)) per 1,000 pregnancies, for women with type 2 diabetes was 346.2 (95% CI (325.5 367.5)) per 1,000 pregnancies, and for women without diabetes was 175.2 (95% CI (174.0, 176.4)) per 1,000 pregnancies. The absolute risk of preeclampsia was 10.3 (95% CI (5.6, 17.2)) per 1,000 pregnancies in women with type 1 diabetes, nearly three times the risk compared to women without diabetes (3.6 (95% CI (3.4, 3.7)) per 1,000 pregnancies, and twice the risk compared to women with type 2 diabetes in pregnancy (5.0 (95% CI (2.4, 9.1)) per 1,000 pregnancies). The risk of major congenital malformations was over three times higher in women with type 1 diabetes (49.2 (95% CI (38.3, 62.1)) per 1,000 pregnancies) when compared to women without diabetes (15.5 (95% CI (15.1, 15.9)) per 1,000 pregnancies) and nearly twice as high compared to women with type 2 diabetes in pregnancy (26.3 (95% CI (19.8, 34.2)) per 1,000 pregnancies) (Figure 8.1).

The absolute risk of an instrumental delivery was similar for women with type 1 diabetes and without diabetes in pregnancy but women with type 2 diabetes had a lower absolute risk of instrumental delivery. Women with type 1 diabetes had an absolute risk of 66.9 (95% CI (54.2, 81.5)) per 1,000 pregnancies compared to the absolute risk of 66.8 (95% CI (66.0, 67.6)) per 1,000 pregnancies for women without diabetes in pregnancy. The absolute risk of instrumental delivery for women with type 2 diabetes was 42.7 (95% CI (34.3, 45.4)) per 1,000 pregnancies, 40% lower than women with type 1 and without diabetes (Figure 8.1 (B)).

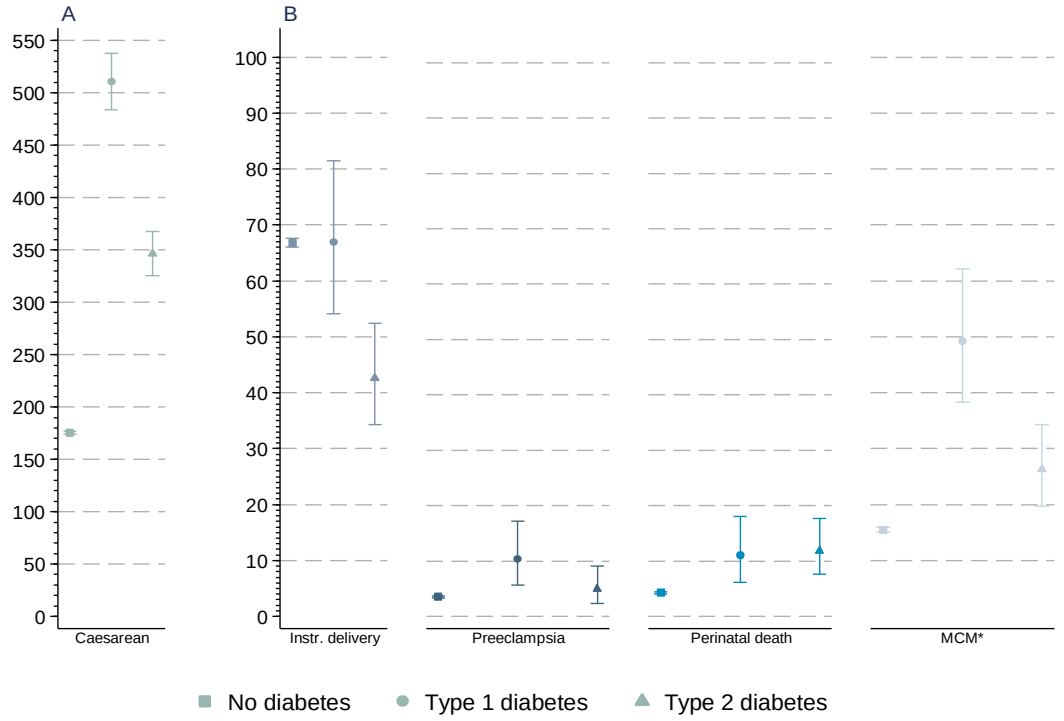
The risk of perinatal death was very similar in women with type 1 and type 2 diabetes: 11.0 (95% CI (6.2, 18.1)) per 1,000 pregnancies and 11.9 (95% CI (7.6, 17.7)) per 1,000 pregnancies, respectively. For both women with type 1 and type 2 diabetes the risk was

approximately two and half times higher than women without diabetes in pregnancy (4.3 (95% CI (4.1, 4.5)) per 1,000 pregnancies (Figure 8.1 (B)).

The pair wise risk difference of each outcome for women with type 1 and type 2 diabetes compared to women without diabetes in pregnancy is displayed in Table 8.2 . The risk of each outcome was higher in women with type 1 and type 2 diabetes for all outcomes, except instrumental delivery for both women with type 1 and type 2 diabetes and preeclampsia for women with type 2 diabetes.

The largest difference was found for caesarean section for women with type 1 diabetes compared to women without diabetes: 334.6 (95% CI (308.0, 361.2)). Followed by the risk difference of caesarean section for women with type 2 diabetes compared to women without diabetes: 169.9 (95% CI (149.1, 190.7)). The risk difference of perinatal death was similar for both women with type 1 and type 2 diabetes compared to women without diabetes: 6.7 (95% CI (1.2, 12.3)) for type 1 diabetics and 7.6 (95% CI (2.9, 17.7)) for type 2 diabetics (Table 8.2).

Figure 8.1: By diabetes status, the absolute risk and 95% confidence interval of (A) Caesarean section, (B) Instrumental delivery, Preeclampsia, Perinatal death and Major congenital malformations



*MCM = Major congenital malformation

Instr. delivery = Instrumental delivery

Table 8.2: The absolute risk and risk difference for each adverse pregnancy outcome by diabetes status

	Absolute risk (95% CI) per 1,000 pregnancies			Risk difference * (95% CI)	
	Not diabetic	**Type 1 diabetes**	**Type 2 diabetes**	**Type 1 diabetes**	**Type 2 diabetes**
Caesarean section	175.2 (174.0, 176.4)	510.7 (483.7, 537.5)	346.2 (325.5, 367.5)	334.6 (308.0, 361.2)	169.9 (149.1, 190.7)
Instrumental delivery	66.8 (66.0, 67.6)	66.9 (54.2, 81.5)	42.7 (34.3, 52.4)	0.2 (-13.1, 13.5)	-24.1 (-33.0, -15.3)
Preeclampsia	3.6 (3.4, 3.7)	10.3 (5.6, 17.2)	5.0 (2.4, 9.1)	6.7 (1.4, 12.1)	1.4 (-1.7, 4.5)
Perinatal death	4.3 (4.1, 4.5)	11.0 (6.2, 18.1)	11.9 (7.6, 17.7)	6.7 (1.2, 12.3)	7.6 (2.9, 12.3)
Major congenital malformations	15.5 (15.1, 15.9)	49.2 (38.4, 62.1)	26.3 (19.8, 34.2)	33.7 (22.2, 45.2)	10.7 (3.7, 17.7)

* Risk difference is calculated between the diabetic group and non-diabetics (type 1 vs not diabetic and type 2 vs not diabetic)

8.4.2 Objective two - Temporal trends in the prevalence of each adverse outcome

For each adverse pregnancy outcome the absolute risk was calculated by diabetes status and calendar period: 2000-2002, 2003-2005, 2006-2008, and 2009-2012 (Figure 8.2 and Figure 8.3). In the first two calendar periods: 2000-02 and 2003-05, the prevalence of caesarean section was similar for women with type 1 and type 2 diabetes and both were much higher than the risk for women without diabetes. In the latter two calendar periods: 2006-08 and 2009-12, the prevalence of caesarean section was highest in women with type 1 diabetes (Figure 8.2). The prevalence of caesarean section for women with type 1 diabetes during pregnancy peaked in the calendar period 2006-2008 at 564.7 (95% CI (510.2, 618.1)) per 1,000 pregnancies, for the other calendar periods in the study the prevalence ranged from 456.4 (95% CI (392.4, 521.6)) to 515.0 (95% CI (436.5, 592.9)) per 1,000 pregnancies. For women with type 2 diabetes during pregnancy the prevalence of caesarean section was highest in the first two calendar periods: 412.7 (95% CI (325.8, 503.8)) per 1,000 pregnancies in 2000-02 and 412.8 (95% CI (356.3, 471.0)) per 1,000 pregnancies 2003-05, the prevalence then fell to 318.6 (95% CI (276.8, 362.6)) per 1,000 pregnancies in 2006-08 and 331.8 (95% CI (303.5, 361.0) per 1,000 pregnancies in 2009-12. For women without diabetes in pregnancy the prevalence of caesarean section delivery increased across the study period: 160.7 (95% CI (157.6, 168.8)) per 1,000 pregnancies in 2000-02 to 186.5 (95% CI (184.4, 188.6)) per 1,000 pregnancies in 2009-12 (Figure 8.2).

For the remaining four pregnancy outcomes the confidence intervals for calendar period prevalence estimates are very wide and overlap for the different diabetic statues. Therefore, I will only describe the temporal trends in prevalence of each outcome in general and not for each diabetes status.

The prevalence of an instrumental delivery increased over the study period for pregnant women, from between 15.9 and 61.8 per 1,000 pregnancies in 2000-02 to between 43.4 and 70.1 per 1,000 pregnancies in 2009-12. The prevalence of preeclampsia remained relatively stable across the study period. There was a slight increase for women with type 1 diabetes, but not a substantially change. At the start of the study period, 2000-02, preeclampsia ranged from 4.0 to 12.0 per 1,000 pregnancies for pregnant women and by the end of the study, 2009-12, this had changed to 3.2 to 14.0 per 1,000 pregnancies. Over the study period the prevalence of perinatal death decreased slightly. In 2000-02

Figure 8.2: Temporal trends in the prevalence and 95% confidence intervals of caesarean section presented by diabetes status and calendar period

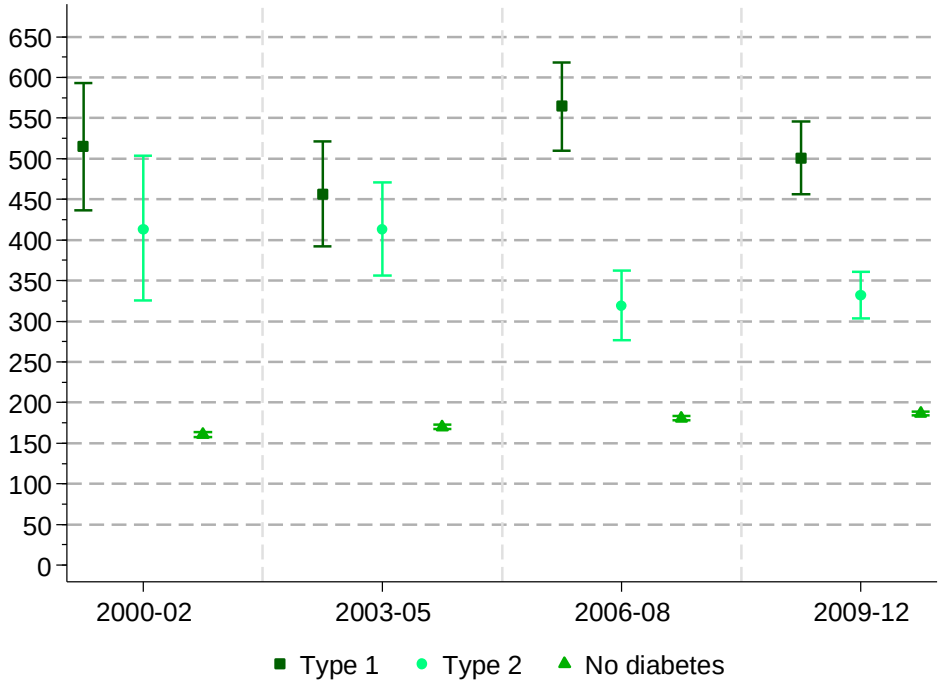
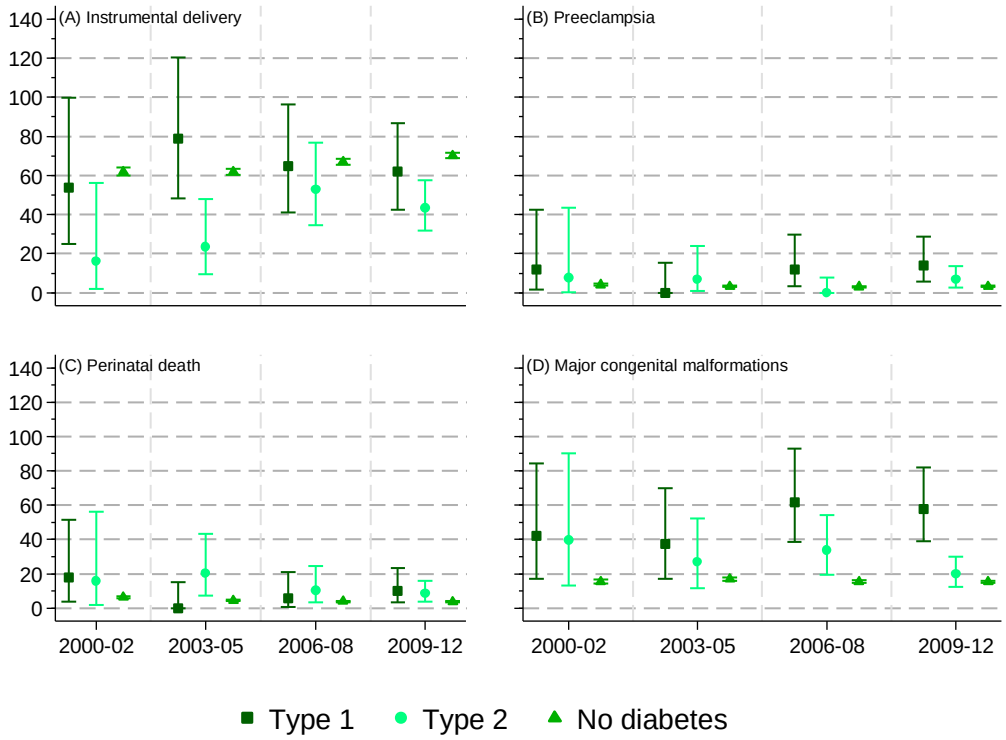


Figure 8.3: Temporal trends in the prevalence and 95% confidence intervals of Instrumental delivery, Preeclampsia, Perinatal death, and Major congenital malformations, presented by diabetes status and calendar period



the prevalence of perinatal death ranged from between 6.4 and 18.0 per 1,000 pregnancies, decreasing to between 3.7 and 10.0 per 1,000 pregnancies in 2009-12.The prevalence of major congenital malformations remained relatively stable across the whole study period. In the first calendar period, 2000-02, the prevalence of major congenital malformations ranged from 15.5 to 41.9 per 1,000 pregnancies. In the final calendar period, 2009-12, the prevalence of major congenital malformations ranged from 15.3 to 57.9 per 1,000 pregnancies. There was a peak in the prevalence of major congenital malformations at 61.8 (95% CI (38.6, 92.9)) per 1,000 pregnancies for women with type 1 diabetes in 2006-08, but this was not substantially different to the other calendar periods (Figure 8.3).

8.4.3 Objective three - Risk of each adverse pregnancy outcome adjusted for maternal demographic and clinical characteristics

The final objective of this study was to calculate risk ratios for each adverse pregnancy outcome adjusting for differences in demographic and clinical characteristics in women with and without pregestational diabetes in pregnancy. As detailed in the methods section the model building had three phases: selection of confounders, complete case analysis, and imputed data analysis. Firstly, I present the confounder selection results for all of the adverse pregnancy outcomes together and then I will present the complete case and imputed data analysis by each adverse pregnancy outcome separately.

8.4.3.1 Confounder selection

The maternal characteristics that were investigated as potential confounders were: maternal age, diastolic blood pressure, overweight, hyperglycaemia, smoking status, alcohol dependence, and Townsend deprivation quintile. For each characteristic a univariate Poisson regression with diabetes status (type 1 compared to not diabetic and type 2 compared to not diabetic) was conducted to identify which potential confounders were associated with diabetes status. The results of the univariate analysis are presented in Appendix IV. All maternal characteristics were found to be associated with diabetes status.

The second step of identifying which maternal characteristics were confounders for each adverse pregnancy outcome was to conduct univariate Poisson regression analysis with each outcome and characteristic. The results for these univariate Poisson regression models are also presented in Appendix IV. The maternal characteristics identified as

Table 8.3: The list of maternal characteristics identified as potential confounders for each adverse pregnancy outcome

Caesarean section	Instrumental delivery	Perinatal death	Preeclampsia	MCM
Maternal age	Maternal age	Maternal age	Maternal age	Maternal age
Diastolic BP		Diastolic BP	Diastolic BP	Diastolic BP
Overweight	Overweight	Overweight		
Hyperglycaemia		Hyperglycaemia	Hyperglycaemia	Hyperglycaemia
Smoking status	Smoking status	Smoking status	Smoking status	Smoking status
		Alcohol		Alcohol *
Townsend score	Townsend score	Townsend score		

* Alcohol– alcohol dependence.
Abbreviations: MCM = major congenital malformation, BP = Blood pressure

potential confounders for each outcome are listed in Table 8.3. In summary: maternal age, and smoking status were associated with all five outcomes. Diastolic blood pressure, and hyperglycaemia were associated with all outcomes apart from instrumental delivery. Overweight, and Townsend deprivation score were only associated with caesarean section, instrumental delivery, and perinatal death and alcohol dependence was only associated with perinatal death, and major congenital malformations (Table 8.3).

The maternal characteristics that were selected as confounders for each adverse pregnancy outcome were those that were associated with diabetes status and the adverse outcome in the univariate Poisson regression models. The final list of selected confounders for each adverse pregnancy outcome is presented in Table 8.3. It was decided a priori that maternal age would be included in all adjusted models as it is an important covariate for all of the outcomes.

In the next sections I will present the results from the adjusted analysis for each adverse pregnancy outcome for both the complete cases, and imputed data.

8.4.3.2 Caesarean section

In the unadjusted univariate Poisson regression model between caesarean section and pregestational diabetes the risk of experiencing a caesarean section delivery was three times higher in women with type 1 diabetes (risk ratio (RR) 2.99 (95% CI (2.73, 3.28)) and over twice as high in women with type 2 diabetes, compared to women without diabetes (RR 2.11 (95% CI (1.92, 2.32)). After adjusting for maternal age, diastolic blood pressure, maternal overweight prior to pregnancy, hyperglycaemia prior to pregnancy, smoking status, and Townsend deprivation score the risk ratio for women with type 1

diabetes compared to women without diabetes decreased to 2.41 (95% CI (2.13, 2.75)) but remained highly significant (p-value<0.001). Whilst the adjusted risk ratio for women with type 2 diabetes compared to women without diabetes decreased to 1.58 (95% CI (1.42, 1.75)), and again remained highly significant (p-value<0.001) (Table 8.4).

The results from the adjusted Poisson regression analysis conducted on the multiple imputed dataset are similar to these produced from the complete cases. The adjusted risk ratios for pregestational diabetes compared to not diabetic reduced slightly, to 2.29 (95% CI (2.06, 2.55)) for women with type 1 diabetes and 1.45 (95% CI (1.32, 1.59)) for women with type 2 diabetes (Table 8.4).

8.4.3.3 Instrumental delivery

For women with type 1 diabetes in pregnancy the risk of an instrumental delivery was 14% lower than women without diabetes in pregnancy (RR 0.86 (95% CI (0.67, 1.11))), and women with type 2 diabetes in pregnancy were at 25% less risk of an instrumental delivery when compared to women without diabetes in pregnancy (RR 0.75 (95% CI (0.59, 0.94))). The confidence interval for women with type 1 included 1, indicating that there is no evidence of an increased risk of instrumental delivery (Table 8.4).

After adjusting for age, overweight, hyperglycaemia, smoking status, and Townsend deprivation score there was no evidence of an association between pregestational diabetes and instrumental delivery. The results from the imputed dataset are comparable to the complete case analysis (Table 8.4).

8.4.3.4 Preeclampsia

There was a substantial difference in the unadjusted risk ratios for preeclampsia in women with type 1 or type 2 diabetes compared to women without diabetes in pregnancy. For women with type 1 diabetes the risk of preeclampsia was nearly three times higher when compared to women without diabetes; risk ratio 2.88 (95% CI (1.49, 5.56)). For women with type 2 diabetes there was no difference when compared to women without diabetes: risk ratio 0.98 (95% CI (0.37, 2.61)) (Table 8.4).

The difference between women with type 1 and type 2 diabetes in the risk of preeclampsia remained after adjusting for: age, diastolic blood pressure, hyperglycaemia, and smoking status. Although both risk ratios reduced and were no longer significantly associated with preeclampsia. For women with type 1 diabetes compared to women without diabetes the

Table 8.4: Unadjusted, adjusted and multiple imputation Poisson regression analysis for the relationship between each adverse pregnancy outcome and pregestational diabetes

		Unadjusted analysis		Adjusted – complete case		Adjusted – imputed data	
		Risk ratio (95% CI)	p-value	Risk ratio (95% CI)	p-value	Risk ratio (95% CI)	p-value
Caesarean section		N = 185,871		N = 185,871		N = 301,536	
	No diabetes	-	<0.001	-	<0.001	-	<0.001
	Type 1	2.99 (2.73, 3.28)		2.41 (2.13, 2.72)		2.29 (2.06, 2.55)	
	Type 2	2.11 (1.92, 2.32)		1.58 (1.42, 1.75)		1.45 (1.32, 1.59)	
Instrumental delivery		N = 284,358		N = 284,358		N = 301,536	
	No diabetes	-	0.02	-	0.08	-	0.2
	Type 1	0.86 (0.67, 1.11)		0.86 (0.67, 1.11)		0.95 (0.75, 1.21)	
	Type 2	0.75 (0.59, 0.94)		0.80 (0.64, 1.01)		0.80 (0.64, 1.01)	
Preeclampsia		N = 195,431		N = 195,431		N = 301536	
	No diabetes	-	0.007	-	0.4	-	0.06
	Type 1	2.88 (1.49, 5.56)		1.58 (0.55, 4.48)		2.49 (1.13, 5.44)	
	Type 2	0.98 (0.37, 2.61)		0.72 (0.24, 2.17)		0.95 (0.41, 2.21)	

		Unadjusted analysis		Adjusted – complete case		Adjusted – imputed data	
		Risk ratio (95% CI)	p-value	Risk ratio (95% CI)	p-value	Risk ratio (95% CI)	p-value
Perinatal death		N = 185,871		N = 185,871		N = 301,536	
	No diabetes	-	<0.001	-	0.003	-	0.01
	Type 1	2.63 (1.36, 5.08)		1.95 (0.84, 4.49)		1.66 (0.73, 3.76)	
	Type 2	3.60 (2.19, 5.91)		2.72 (1.53, 4.85)		2.37 (1.32, 5.92)	
Major congenital malformations		N = 195,431		N = 195,431		N = 301,536	
	No diabetes	-	<0.001	-	0.001	-	<0.001
	Type 1	3.37 (2.53, 4.50)		2.29 (1.49, 3.51)		2.35 (1.61, 3.43)	
	Type 2	1.48 (1.01, 2.16)		1.19 (0.78, 1.81)		1.42 (1.01, 2.00)	

risk ratio of preeclampsia was 1.58 (95% CI (0.55, 4.48)) and for women with type 2 diabetes compared to women without diabetes in pregnancy the risk ratio was 0.72 (95% CI (0.24, 2.17)) (Table 8.4).

In the impute analysis the risk ratio estimate for preeclampsia in women with type 1 diabetes compared to women without diabetes increased to 2.49 (95% CI (1.13, 5.44)). The risk ratio estimate for preeclampsia in women with type 2 diabetes compared to women without diabetes also increased to 0.95 (95% CI (0.41, 2.21)). There was some evidence of a significant association between diabetes in pregnancy and preeclampsia in the multiple imputed data (p=0.06) (Table 8.4).

8.4.3.5 Perinatal death

For women with type 1 diabetes in pregnancy the unadjusted risk of perinatal death was over two and a half times higher when compared to women without diabetes in pregnancy: RR 2.63 (95% CI (1.36, 5.08)). Women with type 2 diabetes in pregnancy had an unadjusted risk of perinatal death that was over three and a half times higher when compared to women without diabetes in pregnancy: RR 3.60 (95% CI (2.19, 5.91)) (Table 8.4).

After adjusting for: maternal age, diastolic blood pressure, maternal overweight, hyperglycaemia, alcohol dependence, smoking status, and Townsend deprivation quintile, the risk ratios for both diabetic types reduced and for women with type 1 diabetes were no longer significantly associated with perinatal death. Women with type 2 diabetes had nearly three times the risk of perinatal death when compared to women without diabetes in pregnancy: the adjusted risk ratio was 2.72 (95% CI (1.53, 4.85)). Whereas, there was no evidence of a difference in the risk of perinatal death for women with type 1 diabetes in pregnancy: adjusted RR 1.95 (95% CI (0.84, 4.49)). The results were slightly reduced in the multiple imputed data. The risk of perinatal death reduced to over twice that of women without diabetes in the imputed model for type 2 diabetes: RR 2.37 (95% CI (1.32, 5.92)) (Table 8.4).

8.4.3.6 Major congenital malformation

Similarly to preeclampsia there was a substantial difference in the risk of major congenital malformations (MCM) for women with type 1 and type 2 diabetes compared to women without diabetes in the unadjusted analysis. Women with type 1 diabetes had a nearly

three and half times the risk (RR 3.37 (95% CI (2.53, 4.50)) when compared to women without diabetes in pregnancy. Women with type 2 diabetes were at nearly 50% increased risk of MCM when compared to women without diabetes in pregnancy: risk ratio 1.48 (95% CI (1.01, 2.16)) (Table 8.4).

After adjusting for age, diastolic blood pressure, hyperglycaemia, smoking status, and alcohol dependence; the risk of major congenital malformations reduced for both women with type 1 and type 2 diabetes. For women with type 1 diabetes compared to women without diabetes the risk ratio of MCM reduced to 2.29 (95% CI (1.49, 3.51)). After adjusting for maternal characteristics women with type 2 diabetes in pregnancy no longer had a statistically increased risk of MCM compared to women without diabetes in pregnancy: risk ratio 1.19 (95% CI (0.78, 1.81)). The results from the imputed data analysis were very comparable to the complete case analysis. The risk of major congenital malformation for women with diabetes increased slightly in the imputed data analysis and was statistically significant for both type 1 and type 2 diabetes; risk ratio 2.35 (95% CI 1.61, 3.43)) for women with type 1 diabetes and 1.42 (95% CI (1.01, 2.00)) for women with type 2 diabetes (Table 8.4).

8.5 Discussion

8.5.1 Summary of results

Women with diabetes were at an increased absolute risk of experiencing any of the five selected adverse outcomes in pregnancy when compared to women without diabetes in pregnancy. Overall women with type 1 diabetes had a higher absolute risk of experiencing all of the five selected adverse outcomes than women with type 2 diabetes.

After adjusting for demographic and clinical maternal characteristics women with type 1 diabetes were at a statistically significant increased risk of caesarean section delivery and major congenital malformations. Women with type 1 diabetes were at highest risk of experiencing caesarean section delivery: risk ratio 2.41 (95% CI (2.13, 2.72)) compared to women without diabetes. Women with type 1 diabetes were at nearly two and a half times the risk of major congenital malformation compared to women without diabetes in pregnancy: risk ratio 2.29 (95% CI (1.53, 4.85)).

After adjusting for maternal demographic and clinical factors women with type 2 diabetes were at a statistically significant increased risk of caesarean section and perinatal death.

Women with type 2 diabetes had 58% increased risk of caesarean section delivery than women without diabetes in pregnancy (RR 1.58 (95% CI (1.42, 1.75))). Women with type 2 diabetes had over two and half times the risk of perinatal death when compared to women without diabetes in pregnancy: risk ratio 2.72 (95% CI (1.53, 4.85)).

8.6 Conclusions

My findings show that women with type 1 and type 2 diabetes are at an increased risk of experiencing adverse pregnancy outcomes. There is still substantial work to be done to reduce the risk of adverse outcomes experienced by women with diabetes in pregnancy and meet the recommendations set out in the St Vincent declaration over twenty years ago.

In the next chapter I will discuss the results and implications of this chapter in further detail. I will link the important results back to the two previous studies and my initial research interests as set out in Chapter 2. I will also discuss the general and specific strengths and limitations for all the studies.

Chapter 9 Discussion

9.1 Summary of results

There were 586,312 pregnancies identified in THIN. Of these 180,064 were removed because they either did not occur between 1st January 1995 and 31st December 2012 or they occurred prior to the mother being 16 years old or they occurred before the practice met data quality criteria. A further 6,255 pregnancies were removed due to unknown diabetes status or unclassified diabetes type. The remaining 400,055 pregnancies to 301,536 mothers made up the pregnancy cohort used throughout this thesis. Pregestational diabetes affected 0.8% (N=3,377) of all pregnancies: type 1 diabetes accounted for 40% (N=1,361) of cases of diabetes in pregnancy.

In the following sections I will highlight the important findings from my PhD, for each of the three studies separately.

9.1.1 Study one – Pregestational diabetes in pregnancy

I found that over the study period the prevalence of pregestational diabetes in pregnancy increased for both type 1 and type 2 diabetes. In the first calendar year of the study period, 1995, the prevalence of pregestational type 1 diabetes in pregnancy was 1.58 per 1,000 pregnancies. By 2012, at the end of the study, the prevalence of type 1 diabetes in pregnancy had increased to 4.34 per 1,000 pregnancies. The prevalence of type 2 diabetes was found to increase at a much faster rate than the prevalence of type 1 diabetes over the same period. In 1995, the prevalence of type 2 diabetes was 2.38 per 1,000 pregnancies, rising to 10.37 per 1,000 pregnancies in 2012. The prevalence of type 2 diabetes increased at an accelerated rate after 2008 until the end of the study period.

In women with type 1 diabetes the most commonly prescribed antidiabetic agent was insulin. Metformin prescribing during pregnancy to women with type 1 diabetes increased over the study period from zero percent in 1995-1997 to 12% in 2010-2012. For women with type 2 diabetes insulin and sulphonylurea prescribing during pregnancy decreased over the study period, whereas metformin prescribing increased.

9.1.2 Study two – Prevalence of adverse maternal and child pregnancy outcomes

The prevalence of congenital malformations and perinatal mortality recorded in THIN is comparable to national figures. In THIN prevalence of caesarean section and instrumental delivery was lower than national figures. Given the last national audit assessing the prevalence of preeclampsia was in 1992, the outdated comparison prevalence makes it difficult to fairly assess whether THIN data is comparable to current national figures. Especially considering my findings show the prevalence of preeclampsia decreased between 1995 and 2012.

Of the five selected outcomes the two delivery outcomes; caesarean section and instrumental delivery, were the most common: affecting 177.22 (95% CI (176.04, 178.40)) and 66.68 (95% CI (65.91, 67.45)) per 1,000 pregnancies respectively. Major congenital malformations affected 15.68 (95% CI (15.30, 16.07)) per 1,000 pregnancies, perinatal death affected 4.34 (95% CI (4.14, 4.55)) per 1,000 pregnancies, and preeclampsia affected 3.59 (95% CI (3.41, 3.78)) per 1,000 pregnancies.

Caesarean section was the only outcome to increase in prevalence substantially over the study period, increasing from 134.6 per 1,000 pregnancies in 1995 to 195.3 per 1,000 pregnancies in 2012. Preeclampsia was the only outcome to decrease in prevalence significantly over the study period, decreasing from 11.1 per 1,000 pregnancies in 1995 to 3.3 per 1,000 pregnancies in 2012. The prevalence of major congenital malformations increased slightly over the study period from 8.7 per 1,000 pregnancies in 1995 to 11.6 per 1,000 pregnancies in 2012. The prevalence of instrumental delivery and perinatal death fluctuated between: 56.9 and 80.5 per 1,000 pregnancies and 3.2 and 6.5 per 1,000 pregnancies, respectively.

9.1.3 Study three – The risk of adverse pregnancy outcomes due to pregestational diabetes in pregnancy

After adjusting for maternal demographic and clinical characteristics women with type 1 diabetes remain at an increased risk of caesarean section delivery and major congenital malformations when compared to women without diabetes. Women with type 1 diabetes had the highest increased risk of caesarean section delivery when compared to women without diabetes, controlling for maternal characteristics: RR 2.41 (95% CI (2.13, 2.72)). Major congenital malformations was the other outcome that women with type 1 diabetes

had a statistically increased risk for compared to women without diabetes: RR 2.29 (95% CI (1.49, 3.51)). Women with type 1 diabetes were not at a statistically significant increased risk of preeclampsia, perinatal death or instrumental delivery compared to women without diabetes in pregnancy.

Women with type 2 diabetes in pregnancy remain at an increased risk of caesarean section and perinatal death when compared to women without diabetes in pregnancy after adjusting for maternal demographic and clinical characteristics. Women with type 2 diabetes had the highest risk of perinatal death when compared to women without diabetes in pregnancy: 2.72 (95% CI (1.53, 4.85)). Caesarean section delivery was the other outcome that had a statistically increased risk among women with type 2 diabetes when compared to women without diabetes in pregnancy: 1.58 (95% CI (1.42, 1.75)). The risk of preeclampsia, major congenital malformations, and instrumental delivery were not statistically different between women with type 2 diabetes and women without diabetes in pregnancy.

Neither women with type 1 diabetes nor women with type 2 diabetes were at a statistically increased risk of instrumental delivery compared to women without diabetes in pregnancy.

9.2 Comparison with current literature

In this section I discuss the main findings from the three studies in relation to the current literature; focussing on the findings from the cohort study. I will discuss in detail: the prevalence of pregestational diabetes in pregnancy and the relationship between pregestational diabetes and adverse pregnancy outcomes.

9.2.1 Prevalence of pregestational diabetes in pregnancy

There were only a few studies that have explored the prevalence of pregestational diabetes in pregnancy in the UK (34,78). Bell *et al* (34) had a similar study setting and population to my PhD cohort with the exception of, the geographic region which was restricted to the North of England and that women were selected from hospitals instead of primary care. Bell *et al* found that there was a modest increase in the prevalence of type 1 diabetes in pregnancy between 1996 and 2004 from 2.9 to 3.3 per 1,000 pregnancies which is very comparable to the prevalence rates I found over the same time period: 2.7 per 1,000 pregnancies in 1996 and 3.0 per 1,000 pregnancies in 2004. The

prevalence of type 2 diabetes in pregnancy based on work by Bell *et al* also described an increase from 0.2 to 1.2 per 1,000 pregnancies between 1996 and 2004. I found that the prevalence of type 2 diabetes in pregnancy increased more significantly over the same time period: 0.5 to 3.1 per 1,000 pregnancies. The difference in the prevalence rates of type 2 diabetes in pregnancy found in this thesis and the work of Bell *et al* may be explained by the fact that a lower proportion of women in the Bell *et al* study were of a non-white ethnic background; only 20% of women with type 2 diabetes were from non-white background in the Bell *et al* study compared to 25% (of known ethnicity) in this thesis. The other UK study from the Confidential Enquiry into Maternal and Child Health (CEMACH) investigated the prevalence of pregestational diabetes over one year, 2002-2003, in hospitals from England, Wales and Scotland (78). CEMACH found that pregestational diabetes occurs in one in every 264 births, of which type 1 diabetes effects 2.7 per 1,000 pregnancies and type 2 diabetes effects 1.0 per 1,000 pregnancies. My findings from the same years are comparable for type 1 diabetes; 3.0 per 1,000 pregnancies in 2002 and 2.6 per 1,000 pregnancies in 2003. But again, I found a higher prevalence of type 2 diabetes; 2.9 per 1,000 pregnancies in 2002 and 3.8 per 1,000 pregnancies in 2003. There was considerable variation in the prevalence of type 2 diabetes found in the different regions of the UK; 1.7 per 1,000 in London and 0.5 per 1,000 in Wales, leading CEAMCH to question whether diabetes in pregnancy is recognised uniformly across the UK (78). The location of practices that contribute data to THIN may be within areas with a higher prevalence of diabetes, THIN is over represented in the South East region of the UK, which may contribute to a higher prevalence of diabetes within THIN when compared to the CEMACH study.

I also found a small number of studies investigating the prevalence of pregestational diabetes in pregnancy from Spain, America, and Canada (72,73,75,76,79), all of the international studies used hospital data. The three studies from American hospitals found that the prevalence of diabetes increased over time (72,73,76). Lawrence *et al* (76) found the prevalence of diabetes increased from 7.6 to 19.0 per 1,000 pregnancies between 1999 and 2005, estimates by diabetes type were not presented. Albrecht *et al* (72) found the overall prevalence of diabetes increased from 34.9 to 54.7 per 1,000 pregnancies, the prevalence of type 1 diabetes increased from 2.4 to 3.3 per 1,000 pregnancies, and the prevalence of type 2 diabetes increased from 0.9 to 4.2 per 1,000 between 1994 and 2004. Gestational diabetes accounted for approximately 85% of all diabetic pregnancies studied by Albrecht *et al* (72). Bardenheier *et al* (73) found the prevalence of pregestational diabetes increased from 6.5 to 8.9 per 1,000 between 2000 and 2010,

estimates by diabetes type were not presented. The prevalence of pregestational diabetes in pregnancy was substantially higher in the three American studies than in this thesis. The Spanish study by de Andres *et al* (79) found the prevalence of pregestational diabetes increased from 2.0 to 2.7 per 1,000 pregnancies between 2001 and 2008, which is lower than the prevalence I found over the same study period. The study from Feig *et al* using administrative health claims data in Canadian hospitals found the prevalence of pregestational diabetes increased from 7.0 to 15.0 per 1,000 pregnancies between 1996 and 2009, which was substantially higher than the prevalence I found but is quite similar to the prevalence found in the three American studies. The prevalence found within the American and Canadian studies are likely to reflect the true rates of diabetes as ascertainment within these populations is more accurate.

9.2.2 Risk of adverse pregnancy outcomes in THIN

9.2.2.1 Caesarean section delivery

I found that women with type 1 diabetes had nearly two and half times the risk of having a caesarean section delivery compared to women without diabetes, adjusting for maternal demographic and clinical characteristics: risk ratio 2.41 (95% CI (2.13, 2.72)). For women with type 2 diabetes compared to women without the diabetes I found the risk of caesarean section delivery was nearly 60% higher after adjusting for maternal demographic and clinical characteristics: risk ratio 1.58 (95% CI (1.42, 1.75)).

There were eight studies that examined caesarean section delivery in my literature review presented in Chapter 2, section 2.2.1 (45–52). Although, only half of these studies made comparisons between either women with and without diabetes (49,50,52) or between women with type 1 and type 2 diabetes (51). Of the studies comparing the risk of caesarean section among women with diabetes to women without diabetes all recruited women with type 1 diabetes only and found a statistically increased risk of caesarean section delivery for women with type 1 diabetes. Evers *et al* and Jensen *et al*, found that women with type 1 diabetes had approximately four times the risk of a caesarean section than women without diabetes in pregnancy (49,50). Persson *et al* found women with type 1 diabetes in pregnancy had over five times higher odds of a caesarean section delivery than women without diabetes in pregnancy: odds ratio 5.31 (95% CI (4.97, 5.69)) (52). These estimates for caesarean section delivery among women with type 1 diabetes are significantly higher than my findings. All of these studies were conducted outside of the UK where the guidance on when to perform a caesarean section delivery may be different

to the UK guidelines. The relative risk of caesarean section delivery among women with type 1 diabetes compared to national data presented by Evers *et al* and Jensen *et* al were unadjusted, these estimates were comparable to my unadjusted rates among women with type 1 diabetes compared to women without diabetes (49,50). The Persson *et al* study is conducted using the Swedish birth registry between 1991 and 2003. The Swedish birth registry captures information on all births within Sweden. Whereas, THIN only captures information on births recorded using diagnostic codes from GP practices that contribute data. THIN has been shown to be representative of the UK population in terms of demographic and some chronic diseases (64–66) but I found that the recording of caesarean section delivery was lower than national figures indicating that I may be underestimating the rate of caesarean section among women with type 1 diabetes in the UK.

The only study from my literature review to include women with type 2 diabetes presented an estimate comparing the risk of caesarean section between women with type 1 and type 2 diabetes and found no difference in the risk: relative risk 1.42 (95% CI (0.99, 2.03)) (51). The Clausen *et al* study had a relatively small sample size, 301 pregnancies, in comparison to THIN and may have lacked power to detect a difference in the risk of caesarean section delivery between women with type 1 and type 2 diabetes. I did not conduct an analysis comparing the risk between women with type 1 and type 2 diabetes, but the confidence intervals for my estimates do not overlap implying there is a significant difference in the risk of caesarean section among the two groups.

I updated my literature search to include studies published since the start of my PhD in 2013. I found one study that investigated caesarean section delivery and pregestational diabetes (96). Owens *et al* found that the prevalence of emergency or elective caesarean section delivery was twice as high among women with type 1 diabetes compared to matched controls; prevalence of emergency and elective caesarean was 29% and 30% among women with type 1 diabetes compared to 16% and 15% in women without diabetes, respectively. They also found that the prevalence of elective caesarean section was twice as high in women with type 2 diabetes compared to controls: 36% compared to 19%, respectively (96).

9.2.2.2 Instrumental delivery

For women with type 1 and type 2 diabetes in pregnancy I found no evidence of a difference in the risk of instrumental delivery when compared to women without diabetes

in pregnancy; in the crude or adjusted analysis. For women with type 1 and type 2 diabetes the risk of instrumental delivery was: 0.86 (95% CI (0.67, 1.11)) and 0.80 (95% CI (0.64, 1.01)) compared to women without diabetes, respectively.

I found four studies that investigated instrumental delivery amongst women with diabetes in my literature review (46–48,52). In the literature the prevalence of instrumental delivery for women with type 1 and type 2 diabetes ranged between 4% and 10%, I found an absolute risk of approximately 7% which was very comparable. Of the four studies I found in my literature review only one estimated the risk of instrumental delivery for women with diabetes in pregnancy (52). Persson *et al*, a study utilising data from the Swedish birth register found that women with type 1 diabetes had 40% higher odds of experiencing an instrumental delivery when compared to women without diabetes in pregnancy: odds ratio 1.41 (95% CI (1.25 to 1.58)) (52). The estimate from my study was in contrast to the findings from Persson *et al* and implied women with type 1 diabetes were at a reduced risk of instrumental delivery, although it was not statistically different to women without diabetes in pregnancy. In THIN the rate of instrumental delivery was very similar among women with and without pregestational diabetes. This may be explained by women with diabetes in pregnancy being more likely to deliver via caesarean section, and therefore no longer at risk of having an instrumental vaginal delivery. I did find that women with diabetes had a significantly higher rate of caesarean section when compared women without diabetes in pregnancy.

9.2.2.3 Preeclampsia

In the complete case analysis I found no evidence that women with type 1 diabetes prior to pregnancy were at an increased risk of experiencing preeclampsia, compared to women without diabetes in pregnancy, after adjusting for maternal demographic and clinical characteristics: RR 1.58 (95% CI (0.55, 4.48)). In the imputed analysis there was evidence that women with type 1 diabetes were at an increased risk of preeclampsia: RR 2.49 (95% CI (1.13, 5.44)). I did not find any evidence that women with type 2 diabetes were at a reduced risk of preeclampsia, compared to women without diabetes in pregnancy, after adjustment: RR 0.72 (95% CI (0.24, 2.17)).

There were six papers that examined preeclampsia amongst women with diabetes (47–52), of which three produced risk estimates (49,51,52). Evers *et al* found that women with type 1 diabetes during pregnancy were 12 times more likely to experience preeclampsia, RR 12.1 (95% CI (9.0, 16.1)), when compared to the general population (49). Persson *et*

al also found that women with type 1 diabetes in pregnancy were at an increased odds of experiencing preeclampsia when compared to the general population, adjusted OR for: mild preeclampsia 4.30 (95% CI (3.83, 4.83)) and severe preeclampsia 5.31 (95% CI (4.97, 5.69)) (52). In comparison to these my risk estimate was much lower and not statistically significant for women with type 1 diabetes in pregnancy. My definition of preeclampsia was a composite definition including pregnancy induced hypertension, preeclampsia, and eclampsia, whereas Evers *et al* and Persson *et al* used much stricter clinical definitions for identifying preeclampsia, that included both hypertension and proteinuria (49,52). Clausen *et al* found that there was no difference in the risk of preeclampsia between women with type 1 and type 2 diabetes in pregnancy: RR 1.07 (95% CI (0.57, 2.00)) (51). I also found that there was no statistical difference in the risk of preeclampsia between women with type 1 and type 2 diabetes as the 95% confidence intervals from my estimates overlap.

9.2.2.4 Perinatal death

I found that women with type 2 diabetes during pregnancy had nearly three times the risk of experiencing perinatal death compared to women without diabetes, after adjusting for maternal demographic and clinical factors; RR 2.72 (95% CI (1.53, 4.85)). Whereas, I found no evidence of a difference in the risk of perinatal death between women with type 1 diabetes and without diabetes in pregnancy, after adjusting; RR 1.95 (95% CI (0.84, 4.49)).

I identified 14 papers that included perinatal mortality as an outcome of interest among women with type 1 and type 2 diabetes (34,43,45–56), of which half calculated the risk or odds of perinatal death for women with diabetes (45,47,49–52,56). Evers *et al* and Jensen *et al* found that women with type 1 diabetes were three and half and four times more likely to experience perinatal mortality than women without diabetes in pregnancy: RR 3.5 (95% CI (1.8, 6.7)) and RR (4.1 (95% CI (2.9, 5.6)) respectively (49,50). Persson *et al* found, similarly, that women with type 1 diabetes had over three times the odds of perinatal death than the general population: OR 3.29 (95% CI (2.50, 4.33)) (52). My unadjusted analysis was more comparable to the current literature than my adjusted analysis. In my unadjusted analysis I found the risk of perinatal mortality for women with type 1 diabetes to be over two and a half times higher and for women with type 2 diabetes to be over three and half times higher when compared to women without diabetes in pregnancy. In addition, I previously found that the rate of perinatal mortality may be under

estimated in THIN when compared to national figures. The Confidential Enquiry into Maternal and Child Health (CEMACH) report found the prevalence of perinatal mortality 7.6 (95% CI (7.4, 7.8)) per 1,000 births compared to 4.34 (95% CI (4.14, 4.55)) per 1,000 births in THIN (see Section 7.5.2). The underestimate of perinatal mortality in THIN may explain some of the difference seen here between my findings and the literature.

None of the studies I found calculated the risk of perinatal death separately for women with type 2 diabetes. It is unclear from the current literature whether women with type 1 and type 2 diabetes have different risks of perinatal mortality. The Diabetes and pregnancy group found that there was no difference in the risk of perinatal death among women with type 1 and type 2 diabetes: RR 1.60 (95% CI (0.65, 3.92)) (47). Clausen *et al* found borderline evidence of a difference in the risk of perinatal death among women with type 1 and type 2 diabetes: RR 4.0 (95% CI (1.0, 15.5)) (51). My findings are more comparable to those of Clausen *et al* than the diabetes and pregnancy group 2003 (47,51).

9.2.2.5 Major congenital malformations

In my multivariate Poisson model, women with type 1 diabetes had over twice the risk of experiencing a major congenital malformation in comparison to women without diabetes in pregnancy: RR 2.29 (95% CI (1.49, 3.51)). In the complete case analysis after adjusting for maternal demographic and clinical factors women with type 2 diabetes were no longer at an increased risk of experiencing major congenital malformations: RR 1.19 (95% CI (0.78, 1.81)). In the imputed analysis, there was some evidence of an increased risk of major congenital malformations in women with type 2 diabetes: 1.42 (95% CI (1.01, 2.00)).

I identified thirteen studies that examined major congenital malformations among women with diabetes (34,43,45,47–53,55,56,58). Of which six produced a risk estimate (45,49–52,58). Hawthorne *et al* and Bell *et al* had the most similar study populations to my own; the study populations for both of these papers were pregnant women recruited from the North of England (45,58). Hawthorne *et al* found that women with diabetes had nearly four times the risk of congenital malformations when compared to the regional rate; RR 3.76 (95% CI (2.00, 7.06)). Bell *et al* found no evidence that women with diabetes were at an increased risk of congenital malformations when compared to the general population: RR 1.4 (95% CI (0.9, 2.2)) (58). The estimate from Bell *et al* was more similar to mine, although they combined women with type 1 and type 2 diabetes, whereas the

estimate from Hawthorne *et al* was higher than either of my estimates for women with type 1 or type 2 diabetes compared to women without diabetes. The observed differences may be explained by a difference in the study populations, as Hawthorne *et al* recruited women from hospitals whereas Bell *et al* and I identified women using primary care records. Jensen *et al*, Evers *et al* and Persson *et al* all only recruited women with type 1 diabetes and found that the risk or odds of congenital malformation was increased in comparison to the general population: RR 1.7 (95% CI (1.3, 2.2)), RR 3.4 (95% CI (3.4, 4.8)), and OR 2.50 (95% CI (2.13, 2.94)), respectively (49,50,52). These estimates are all comparable to mine for women with type 1 diabetes in comparison to women without diabetes in pregnancy.

9.3 Strengths and limitations

One of the main strengths of THIN is the size of the database; there are nearly 4 million active patients in THIN from 587 practices spread across England, Wales, Scotland, and Northern Ireland. The THIN pregnancy cohort contains nearly 600,000 pregnancies to over 400,000 women and spans nearly two decades. The final cohort used for this PhD contained 400,055 pregnancies between 1995 and 2012, with pregestational diabetes affecting 0.8% (n=3,377).

Access to primary care is free in the UK, and nearly all residents in the UK are registered with a GP. Previous studies have demonstrated that THIN is approximately representative of the UK population (64). For women the first point of contact with a health care professional upon discovering they are pregnant is often their GP. Therefore, selection bias is likely to be much lower in THIN when compared to populations selected from hospitals or pregnancy registries.

A second strength of THIN data and this study is that THIN contains real life real time data. Data is captured during consultations with practice staff so there is limited recall bias and all prescriptions issued are automatically recorded, ensuring complete records. Being able to access longitudinal electronic health records meant I was able to identify pregnancies affected by diet controlled type 2 diabetes as well as medication controlled type 2 diabetes and type 1 diabetes. I was also able to capture information on potential confounding maternal factors; such as smoking, alcohol dependence, and BMI.

Finally, GPs are generally considered to be the gateway of the NHS, as patients need to be referred to secondary care by their GP. THIN will therefore, include referral letters and discharge letters from secondary care units. These letters will include any diagnosis made and treatments.

As I have previously stated in Chapter 4, there are a few limitations to THIN. The main limitation of THIN is that the database was created for patient management which leads to patient information not being recorded unless it is important to patient care. I found that there was a large amount of missing data for body mass index prior to pregnancy and ethnicity. This means that potentially important covariates may not be available for analysis due to the amount of missing data. I tried to combat the missing data by using multiple imputation methods and found that the complete case and imputed data analyses are very similar.

A second limitation of THIN was the lack of linkage to secondary or specialty care. When a woman with diabetes is referred to any clinic outside of her general practice the care and treatment she receives there is communicated to the practice via letter. This information may be recorded in THIN using Read or AHD codes if the practice regularly codes discharge letters, otherwise the information may be recorded using free text. Unless the free text is anonymised this information is not accessible to researchers.

A third limitation of THIN was the algorithm used to identify pregnancies in the database. Pregnancies ending in miscarriage or termination are excluded by the algorithm as it is difficult to accurately identify the timing and duration of these pregnancies. This could have led to a selection bias as pregnancies ending in termination (spontaneously or induced) would not be documented. Women with diabetes are at an increased risk of experiencing a spontaneous termination and major congenital malformations when compared to women without diabetes in pregnancy (46,52,58). This possible selection bias may have resulted in the risk of major congenital malformations for women with diabetes in pregnancy being under estimated in this project.

This study has demonstrated that the effect of diabetes in pregnancy can be examined without several of the limitations that effect other study designs, such as including women with type 2 diabetes and being able to differentiate between type 1 and type 2 diabetes.

9.4 Clinical implications

The increase in prevalence of type 1 and type 2 diabetes in pregnancy from the first study of this PhD, especially the acceleration over the last few years of the study, should be of special concern to primary care doctors who have to be prepared to work more closely with secondary care on timely management of women with this problem.

This PhD excluded women with gestational diabetes and diabetes first recognised in pregnancy and as such may have underestimated the problem of type 2 diabetes in pregnancy. Diabetes UK (97) estimate that nearly one in every 70 people are affected by undiagnosed type 2 diabetes and are therefore not receiving the care they need. Women with pregestational diabetes are advised to retain good glycaemic control prior to conception and during pregnancy to reduce the risk of adverse outcomes. I found that women with type 1 diabetes in pregnancy had poorer glycaemic control prior to pregnancy when compared to the general population and women with type 2 diabetes. This may be due to women with type 1 diabetes being younger and having a longer duration of disease when compared to women with type 2 diabetes. The poorer glycaemic control of women with type 1 diabetes prior to pregnancy compared to women with type 2 diabetes needs particular attention in terms of its risk to the pregnancy and the baby. It is known that two thirds of women with pregestational diabetes receive suboptimal preconception care (8). With the increasing prevalence seen in primary care, general practitioners can play a pivotal role in delivering preconception care to reduce the risk of adverse outcomes (98–100). This can include both preventive management for all women with diabetes of child bearing age and more specific management of diabetes during pregnancy.

There is an established link between diabetes in pregnancy and adverse pregnancy outcomes; including congenital anomalies, perinatal mortality, spontaneous abortion, and delivery by caesarean section (34,53). The findings from my third PhD study show that women with type 1 and type 2 diabetes remain to be at a heightened risk of experiencing adverse pregnancy outcomes when compared to women without diabetes in pregnancy. There is still substantial work to be done to reduce the risk of adverse outcomes experienced by women with diabetes in pregnancy and meet the recommendations set out in the St Vincent declaration over twenty years ago.

My findings show that women with type 2 diabetes have an increased risk of adverse pregnancy outcomes when compared to women without diabetes in pregnancy but not to the same level as women with type 1 diabetes in pregnancy. In the first of my PhD studies I found that women with type 2 diabetes had better glycaemic control prior to pregnancy than women with type 1 diabetes. In this cohort women with type 2 diabetes also had shorter duration of diabetes prior to pregnancy than women with type 1 diabetes. Soon after diagnosis individuals with diabetes will be offered structured education to help them regain control of their blood glucose concentrations and their diabetes will not have had time to progress, meaning they have fewer complications. These characteristics may help explain why the women with type 2 diabetes had a lower risk of adverse pregnancy outcomes then women with type 1 diabetes. Type 2 diabetes is now being diagnosed much earlier in childhood and adolescents than previously seen, and the risk of adverse outcomes in pregnancy may increase to match that of women with type 1 diabetes in the future.

I found that women with pregestational diabetes are at an increased risk of having a caesarean section delivery; 51% of women type 1 diabetes and 36% of women with type 2 diabetes from the PhD pregnancy cohort. Without information on the indication for caesarean section delivery and without being able to distinguish between elective and emergency caesareans in THIN it is difficult to understand what is driving the substantial increase in risk of caesarean section delivery for women with diabetes.

9.5 UK policy changes post the St. Vincent declaration

The UK government representative at the St Vincent declaration in 1989 agreed upon five recommendations to improve the diagnoses, care, and outcome for people living with diabetes. In particular the fifth recommendation was to improve the pregnancy outcomes for women with diabetes to correspond to women without diabetes (37). Changes to clinical guidelines would be required for the recommendations of the St Vincent declaration to be implemented within the UK. Since the St Vincent declaration there have been a number of adaptions to policy and guidelines for health practitioners caring for pregnant women that may have affected the prevalence of adverse pregnancy outcomes.

9.5.1 Major congenital malformations

In 1991, two years after the St Vincent declaration, an important randomised controlled study into the role of folic acid in preventing the development of neural tube defects was published by the Medical Research Council (101). The study found that 72% (95% CI (29%, 88%)) of neural tube defects could be prevented by taking 4mg of folic acid daily before the start of pregnancy and up to 12 weeks gestation. All women were recommended to take 400 micrograms of folic acid when they plan on becoming pregnant or as soon as they find out they are pregnant (36). In March 2008 NICE published guidance on Maternal and child nutrition (PH11) (102). Health professionals were advised to prescribe 5 milligrams of folic acid to women at higher risk of having a baby with a neural tube defect in the early phases of pregnancy. Women were considered at higher risk if they:

- Or their partner had a neural tube defect
- Had a previous baby with a neural tube defect
- Or their partner had a family history of neural tube defects
- Have diabetes.

The recommendations remained the same for women with diabetes in pregnancy in updated NICE guidance in 2017 (103).

I found that the temporal trends in the prevalence of major congenital malformations did not materially alter for women with and without pregestational diabetes between 2000 and 2012 (see Figure 8.3 (D)). There was a small reduction in the prevalence of major congenital malformations in women with type 1 and type 2 diabetes between the periods 2006-08 and 2009-12 this reduction may be attributed to the introduction of higher daily dose of folic acid, but the confidence intervals overlap indicating a non-significant reduction.

Using THIN data it would be possible to investigate how many women with diabetes in pregnancy received a prescription for 5 milligrams of folic acid daily before conception and up to the first 12 weeks gestation. Using this information I would stratify the analysis into women with diabetes that did and did not receive at least on prescription for folic acid to investigate whether the prevalence of major congenital malformations is different in these groups. It would be interesting, if numbers allowed, to also investigate whether the

prevalence of neural tube defects decreased over the study period and to investigate whether there was any differential by timing and duration of folic acid prescription. A Cochrane review was conducted in 2015 to investigate whether supplementation with folic acid had an effect on all major congenital malformations not just neural tube defects (104). The review included five trials and included 7,391 women. Whilst the review confirmed the findings of a protective effect of folic acid in relation to neural tube defects it did not find evidence of an effect (protective or negative) on other congenital malformations (104).

9.5.2 Preeclampsia

Women at high risk of pre-eclampsia have been advised to take 75mg of aspirin daily from 12 weeks gestation until the birth of the baby since 2010. Women with type 1 and type 2 diabetes are considered to be in the high risk group. I did not find a reduction in the prevalence of pregnancy induced hypertension or preeclampsia since 2010. Although, the introduction of this advice occurred in the final years of my study period so I may not have a long enough study window to study the effect of this advice.

9.5.3 Caesarean section

The caesarean section rate of England is currently 27.1% and is rising (105), a planned VBAC (virginal delivery after caesarean section delivery) is a safe strategy to stop the rising rate of caesarean section delivery (106). The Royal College of Obstetricians and Gynaecologists (RCOG) published guidelines in 2007 setting out the different options for delivery following a previous caesarean section. VBAC is suitable in the majority of women but there are a number of contraindications for VBAC. These are namely: previous uterine rupture or classical caesarean scar, and placenta praevia. I did not find that the prevalence of caesarean section delivery reduced in the time period since this guidance was published in 2007. Instead I found that the prevalence of caesarean section delivery increased at a steady rate from 2003 to 2012 in the general pregnancy population (Figure 7.2), with no differential in the trend for women with and without diabetes (Figure 8.2).

9.6 Further research

At the start of my PhD I was really interested to see how glycaemic control prior to and at the start of pregnancy affected the risk of adverse outcomes for women with

pregestational diabetes. Having now assessed the impact pregestational diabetes had on five pregnancy outcomes I would like to take forward this research by examining whether the risk is modified by level of glycaemic control prior to pregnancy. Unfortunately, there was substantial missing data in the recording of glycaemic control in THIN. Therefore, to take this research question forward a data source with this information available or cohort study would have to be used, possibly in combination with THIN to investigate the impact of glycaemic control.

One of the important findings from my work was the high prevalence of caesarean section delivery among women with diabetes, in particular women with type 1 diabetes. I found that women with type 1 diabetes had over twice the risk and women with type 2 diabetes had 1.50 times the risk of a caesarean section when compared to women without diabetes in pregnancy. This finding persisted after adjusting for clinical and demographic covariates. I would be interested to explore whether a woman's diabetic status in pregnancy was an independent indicator for caesarean section delivery or whether there were circumstances not recorded in primary care, for example: estimated foetal weight >4000g or foetal distress during labour, that are influencing the delivery mode. By linking these data to hospital records and distinguishing between elective and emergency caesareans the primary indication for caesarean section delivery could be investigated.

Finally, my thesis concentrated on the effect of pregestational diabetes on adverse pregnancy outcomes. There is another type of diabetes mellitus that affects pregnancy; gestational diabetes. It would be interesting to investigate whether women with gestational diabetes in THIN have similar risk of adverse pregnancy outcomes as women with pregestational diabetes. This would help to better understand the aetiology of gestational diabetes.

9.7 Conclusion

The recommendation relating to the experience of pregnancy for women with diabetes in the St. Vincent declaration has not been met nearly 30 years later. Women with diabetes in pregnancy are still experiencing higher rates of adverse outcomes when compared to women without diabetes in pregnancy. After adjusting for maternal demographic and clinical characteristics, women with type 1 diabetes remain at an increased risk of caesarean section delivery and major congenital malformations and women with type 2

diabetes remain at increased risk of caesarean section and perinatal death when compared to women without diabetes in my project.

The route to improving pregnancy outcomes for women with diabetes is improved preconception counselling and glycaemic control; the risk of an adverse outcome is halved with each percentage reduction in HbA_{1c} prior to pregnancy (107). Studies have shown that in selected populations with specialist care from preconception right through to delivery women with diabetes can experience a normal pregnancy (43). But this needs to be replicated in all health care settings and not just in specialist care facilities. NICE guidelines recommend that pre-pregnancy care should be incorporated into routine diabetes consultations from adolescence. General Practices could include discussion on pregnancy planning as part of the annual diabetes review with patients. In the 2016 National Pregnancy In Diabetes Annual Report only one in twelve women had achieved good glycaemic control (HbA_{1c}<48mmol/mol), were taking 5mg of folic acid and had stopped taking contraindicated medications prior to conception (108). This indicates that women with diabetes, in collaboration with their health care providers, can do more to improve the management of their diabetes prior to becoming pregnant leading to the reduction of adverse pregnancy outcomes.

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Appendix I. Literature review search terms

Population: TS = (pregnancy OR pregnant)

Exposure: TS = diabet* AND NOT “gestational diabetes”

Estimates: TS = (rate OR risk OR prevalence OR incidence OR odds OR estimate)

Caesarean section search terms

Outcome: TS = (caesarean OR cesarean OR caesarian OR c-section OR "surgical birth" OR "surgical delivery" OR "abdominal delivery")

Instrumental delivery search terms

Outcome: TS = (forcep* OR ventouse OR “instrumental delivery”)

Perinatal death search terms

Outcome: TS = ("perinatal death" OR "perinatal mortality" OR "neonatal death" OR "neonatal mortality" OR "antenatal death" OR "antenatal mortality" OR stillbirth OR stillborn OR "still birth" OR "still born")

Preeclampsia search terms

Outcome: TS = ("preeclampsia" OR "pre-eclampsia" OR "gestational hypertension" OR "maternal hypertension" OR "high blood pressure in pregnancy" OR "protein in the urine" OR "Proteinuria" OR "eclampsia")

Major congenital malformations search terms

Outcome: TS = ("congenital malformation*" OR "congenital anomali*" OR "birth defect*" OR "congenital disorder*" OR "congenital disease")

Appendix II. Diabetes mellitus code list

9.8 Read codes used to identify diabetes mellitus

Read code	Description
13AB.00	Diabetic lipid lowering diet
13AC.00	Diabetic weight reducing diet
13B1.00	Diabetic diet
1434.00	H/O: diabetes mellitus
14F4.00	H/O: Admission in last year for diabetes foot problem
1IA..00	No evidence of diabetic nephropathy
2BBF.00	Retinal abnormality - diabetes related
2BBJ.00	O/E - no right diabetic retinopathy
2BBK.00	O/E - no left diabetic retinopathy
2BBL.00	O/E - diabetic maculopathy present both eyes
2BBM.00	O/E - diabetic maculopathy absent both eyes
2BBP.00	O/E - right eye background diabetic retinopathy
2BBQ.00	O/E - left eye background diabetic retinopathy
2BBR.00	O/E - right eye preproliferative diabetic retinopathy
2BBS.00	O/E - left eye preproliferative diabetic retinopathy
2BBT.00	O/E - right eye proliferative diabetic retinopathy
2BBV.00	O/E - left eye proliferative diabetic retinopathy
2BBW.00	O/E - right eye diabetic maculopathy
2BBX.00	O/E - left eye diabetic maculopathy
2BBk.00	O/E - right eye stable treated proliferated diabetic retinopathy
2BBl.00	O/E - left eye stable treated proliferated diabetic retinopathy
2BBo.00	O/E - sight threatening diabetic retinopathy
2BBr.00	Impair vision due diabetic retinopathy
2G51000	Foot abnormality - diabetes related
2G5A.00	O/E - Right diabetic foot at risk
2G5B.00	O/E - Left diabetic foot at risk
2G5C.00	Foot abnormality - diabetes related
2G5E.00	O/E - Right diabetic foot at low risk
2G5F.00	O/E - Right diabetic foot at moderate risk
2G5G.00	O/E - Right diabetic foot at high risk
2G5H.00	O/E - Right diabetic foot - ulcerated
2G5I.00	O/E - Left diabetic foot at low risk
2G5J.00	O/E - Left diabetic foot at moderate risk
2G5K.00	O/E - Left diabetic foot at high risk
2G5L.00	O/E - Left diabetic foot - ulcerated
2G5V.00	O/E - right chronic diabetic foot ulcer
2G5W.00	O/E - left chronic diabetic foot ulcer

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Read code	Description
2G5d.00	O/E - Left diabetic foot at increased risk
2G5e.00	O/E - Right diabetic foot at increased risk
3881.00	Education score - diabetes
3882.00	Diabetes well being questionnaire
3883.00	Diabetes treatment satisfaction questionnaire
42W..00	Hb. A1C - diabetic control
42WZ.00	Hb. A1C - diabetic control NOS
42c..00	HbA1 - diabetic control
661M400	Diabetes self-management plan agreed
661N400	Diabetes self-management plan review
66A..00	Diabetic monitoring
66A1.00	Initial diabetic assessment
66A2.00	Follow-up diabetic assessment
66A3.00	Diabetic on diet only
66A4.00	Diabetic on oral treatment
66A5.00	Diabetic on insulin
66A8.00	Has seen dietician - diabetes
66A9.00	Understands diet - diabetes
66AA.11	Injection sites - diabetic
66AD.00	Fundoscopy - diabetic check
66AG.00	Diabetic drug side effects
66AH.00	Diabetic treatment changed
66AH000	Conversion to insulin
66AI.00	Diabetic - good control
66AJ.00	Diabetic - poor control
66AJ.11	Unstable diabetes
66AJ100	Brittle diabetes
66AJz00	Diabetic - poor control NOS
66AK.00	Diabetic - cooperative patient
66AL.00	Diabetic-uncooperative patient
66AM.00	Diabetic - follow-up default
66AN.00	Date diabetic treatment start
66AO.00	Date diabetic treatment stopped
66AP.00	Diabetes: practice programme
66AQ.00	Diabetes: shared care programme
66AQ000	Unsuitable for diabetes year of care programme
66AQ100	Declined consent for diabetes year of care programme
66AR.00	Diabetes management plan given
66AS.00	Diabetic annual review
66AT.00	Annual diabetic blood test
66AU.00	Diabetes care by hospital only
66AV.00	Diabetic on insulin and oral treatment
66AW.00	Diabetic foot risk assessment
66AX.00	Diabetes: shared care in pregnancy - diabetology and obstetrics

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Read code	Description
66AY.00	Diabetic diet - good compliance
66AZ.00	Diabetic monitoring NOS
66Aa.00	Diabetic diet - poor compliance
66Ab.00	Diabetic foot examination
66Ac.00	Diabetic peripheral neuropathy screening
66Af.00	Patient diabetes education review
66Ai.00	Diabetic 6 month review
66Ak.00	Diabetic monitoring - lower risk albumin excretion
66Al.00	Diabetic monitoring - higher risk albumin excretion
66An.00	Diabetes type 1 review
66Ao.00	Diabetes type 2 review
66Aq.00	Diabetic foot screen
66As.00	Diabetic on subcutaneous treatment
66At.00	Diabetic dietary review
66At000	Type I diabetic dietary review
66At011	Type 1 diabetic dietary review
66At100	Type II diabetic dietary review
66At111	Type 2 diabetic dietary review
66Au.00	Diabetic erectile dysfunction review
66Av.00	Diabetic assessment of erectile dysfunction
66Az.00	High risk of diabetes mellitus annual review
66b1.00	Diabetic monitoring not required
6761.00	Diabetic pre-pregnancy counselling
679L.00	Health education - diabetes
679L000	Education in self management of diabetes
679R.00	Patient offered diabetes structured education program
67D8.00	Provision of diabetes clinical summary
67IJ100	Pre-conception advice for diabetes mellitus
68A7.00	Diabetic retinopathy screening
68A9.00	Diabetic retinopathy screening offered
68AB.00	Diabetic digital retinopathy screening offered
7276.00	Pan retinal photocoagulation for diabetes
889A.00	Diabetes mellitus insulin-glucose infusion acute myocardial in
8A12.00	Diabetic crisis monitoring
8A13.00	Diabetic stabilisation
8B3l.00	Diabetes medication review
8BL2.00	Patient on maximal tolerated therapy for diabetes
8CA4100	Pt advised re diabetic diet
8CMW700	Diabetes clinical pathway
8CP2.00	Transition of diabetes care options discussed
8CR2.00	Diabetes clinical management plan
8CS0.00	Diabetes care plan agreed
8H2J.00	Admit diabetic emergency
8H3O.00	Non-urgent diabetic admission

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Read code	Description
8H4F.00	Referral to diabetologist
8H4e.00	Referral to diabetes special interest general practitioner
8H7C.00	Refer, diabetic liaison nurse
8H7f.00	Referral to diabetes nurse
8H7r.00	Refer to diabetic foot screener
8HBG.00	Diabetic retinopathy 12 month review
8HBH.00	Diabetic retinopathy 6 month review
8HHy.00	Referral to diabetic register
8HKE.00	Diabetology D.V. requested
8HLE.00	Diabetology D.V. done
8HME.00	Listed for Diabetology admission
8HTE100	Referral to community diabetes clinic
8HTe.00	Referral to diabetes preconception counselling clinic
8HTi.00	Referral to multidisciplinary diabetic clinic
8HTk.00	Referral to diabetic eye clinic
8HVU.00	Private referral to diabetologist
8Hg4.00	Discharged from care of diabetes specialist nurse
8HgC.00	Discharged from diabetes shared care programme
8Hj1.00	Family/carer referral to diabetes structured education
8Hj3.00	Referral to DAFNE diabetes structured education programme
8Hl1.00	Referral for diabetic retinopathy screening
8Hl4.00	Referral to community diabetes specialist nurse
8Hlc.00	Referral to community diabetes service
8I3W.00	Diabetic foot examination declined
8I3X.00	Diabetic retinopathy screening refused
8I57.00	Patient held diabetic record declined
8I6F.00	Diabetic retinopathy screening not indicated
8I6G.00	Diabetic foot examination not indicated
8I81.00	Did not complete diabetes structured education programme
8I82.00	Did not complete DAFNE diabetes structured education
8IAs.00	Diabetic dietary review declined
8IE2.00	Diabetes care plan declined
8IEQ.00	Referral to community diabetes specialist nurse declined
918T.00	Diabetes key contact
9360.00	Patient held diabetic record issued
93C4.00	Patient consent given for addition to diabetic register
9M00.00	Informed consent for diabetes national audit
9M10.00	Informed dissent for diabetes national audit
9N0m.00	Seen in diabetic nurse consultant clinic
9N0n.00	Seen in community diabetes specialist clinic
9N0o.00	Seen in community diabetic specialist nurse clinic
9N1Q.00	Seen in diabetic clinic
9N1i.00	Seen in diabetic foot clinic
9N1o.00	Seen in multidisciplinary diabetic clinic

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Read code	Description
9N1v.00	Seen in diabetic eye clinic
9N2d.00	Seen by diabetologist
9N2i.00	Seen by diabetic liaison nurse
9N4I.00	DNA - Did not attend diabetic clinic
9N4p.00	Did not attend diabetic retinopathy clinic
9NM0.00	Attending diabetes clinic
9NN8.00	Under care of diabetologist
9NN9.00	Under care of diabetes specialist nurse
9NND.00	Under care of diabetic foot screener
9NiA.00	Did not attend diabetes structured education programme
9NiC.00	Did not attend DAFNE diabetes structured education programme
9NiZ.00	Did not attend diabetes foot screening
9Nl4.00	Seen by general practitioner special interest in diabetes
9OL..00	Diabetes monitoring admin.
9OL..11	Diabetes clinic administration
9OL1.00	Attends diabetes monitoring
9OL2.00	Refuses diabetes monitoring
9OL3.00	Diabetes monitoring default
9OL4.00	Diabetes monitoring 1st letter
9OL5.00	Diabetes monitoring 2nd letter
9OL6.00	Diabetes monitoring 3rd letter
9OL7.00	Diabetes monitor.verbal invite
9OL8.00	Diabetes monitor.phone invite
9OL9.00	Diabetes monitoring deleted
9OLA.00	Diabetes monitor. check done
9OLA.11	Diabetes monitored
9OLC.00	Family/carer attended diabetes structured education p
9OLD.00	Diabetic patient unsuitable for digital retinal photo
9OLF.00	Diabetes structured education programme completed
9OLH.00	Attended DAFNE diabetes structured education programme
9OLJ.00	DAFNE diabetes structured education programme completed
9OLL.00	XPERT diabetes structured education programme completed
9OLM.00	Diabetes structured education programme declined
9OLN.00	Diabetes monitor invitation by SMS (short message service)
9OLZ.00	Diabetes monitoring admin. NOS
9Oy..00	Diabetes screening administration
9b92000	Diabetic medicine
9h4..00	Exception reporting: diabetes quality indicators
9h41.00	Excepted from diabetes quality indicators: Patient unsuitable
9h42.00	Excepted from diabetes quality indicators: Informed decent
9h43.00	Excepted from diabetes quality indicators: service unavailable
9m0..00	Diabetic retinopathy screening administrative status
9m00.00	Eligible for diabetic retinopathy screening
9m01.00	Ineligible for diabetic retinopathy screening

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Read code	Description
9m02.00	Eligible temp inactivity diabetes ret screening
9m03.00	Eligible perm inactivity diabetes ret screening
9m04.00	Excluded from diabetic retinopathy screening
9m05.00	Excluded from diabetic retinopathy screening as moved
9m06.00	Excluded from diabetic retinopathy screening as decease
9m07.00	Excluded diabetic retinopathy screen as under care ophthalmic
9m08.00	Excluded diabetes retinopathy screening as blind
9m0A.00	Declined diabetic retinopathy screening
9m0B.00	Ex diabetes retinopathy screening no contact details
9m0C.00	Excluded from diabetic retinopathy screen as terminal
9m0D.00	Excluded from diabetic retinopathy screen as learn dis
9m0E.00	Excluded from diabetic retinopathy screen physical di
C10..00	Diabetes mellitus
C100.00	Diabetes mellitus with no mention of complication
C100000	Diabetes mellitus, juvenile type, no mention of complication
C100011	Insulin dependent diabetes mellitus
C100100	Diabetes mellitus, adult onset, no mention of complication
C100111	Maturity onset diabetes
C100112	Non-insulin dependent diabetes mellitus
C100z00	Diabetes mellitus NOS with no mention of complication
C101.00	Diabetes mellitus with ketoacidosis
C101000	Diabetes mellitus, juvenile type, with ketoacidosis
C101100	Diabetes mellitus, adult onset, with ketoacidosis
C101y00	Other specified diabetes mellitus with ketoacidosis
C101z00	Diabetes mellitus NOS with ketoacidosis
C102.00	Diabetes mellitus with hyperosmolar coma
C102000	Diabetes mellitus, juvenile type, with hyperosmolar c
C102100	Diabetes mellitus, adult onset, with hyperosmolar com
C102z00	Diabetes mellitus NOS with hyperosmolar coma
C103.00	Diabetes mellitus with ketoacidotic coma
C103000	Diabetes mellitus, juvenile type, with ketoacidotic c
C103100	Diabetes mellitus, adult onset, with ketoacidotic com
C103y00	Other specified diabetes mellitus with coma
C103z00	Diabetes mellitus NOS with ketoacidotic coma
C104.00	Diabetes mellitus with renal manifestation
C104.11	Diabetic nephropathy
C104000	Diabetes mellitus, juvenile type, with renal manifest
C104100	Diabetes mellitus, adult onset, with renal manifestation
C104y00	Other specified diabetes mellitus with renal complication
C104z00	Diabetes mellitus with nephropathy NOS
C105.00	Diabetes mellitus with ophthalmic manifestation
C105000	Diabetes mellitus, juvenile type, + ophthalmic manifestation
C105100	Diabetes mellitus, adult onset, + ophthalmic manifest
C105y00	Other specified diabetes mellitus with ophthalmic com

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Read code	Description
C105z00	Diabetes mellitus NOS with ophthalmic manifestation
C106.00	Diabetes mellitus with neurological manifestation
C106.11	Diabetic amyotrophy
C106.12	Diabetes mellitus with neuropathy
C106.13	Diabetes mellitus with polyneuropathy
C106000	Diabetes mellitus, juvenile, + neurological manifestation
C106100	Diabetes mellitus, adult onset, + neurological manifestation
C106y00	Other specified diabetes mellitus with neurological complication
C106z00	Diabetes mellitus NOS with neurological manifestation
C107.00	Diabetes mellitus with peripheral circulatory disorder
C107.11	Diabetes mellitus with gangrene
C107.12	Diabetes with gangrene
C107000	Diabetes mellitus, juvenile +peripheral circulatory disorder
C107100	Diabetes mellitus, adult, + peripheral circulatory disorder
C107200	Diabetes mellitus, adult with gangrene
C107300	IDDM with peripheral circulatory disorder
C107400	NIDDM with peripheral circulatory disorder
C107y00	Other specified diabetes mellitus with peripheral circulatory complication
C107z00	Diabetes mellitus NOS with peripheral circulatory dis
C108.00	Insulin dependent diabetes mellitus
C108.11	IDDM-Insulin dependent diabetes mellitus
C108.12	Type 1 diabetes mellitus
C108.13	Type I diabetes mellitus
C108000	Insulin-dependent diabetes mellitus with renal complication
C108011	Type I diabetes mellitus with renal complications
C108012	Type 1 diabetes mellitus with renal complications
C108100	Insulin-dependent diabetes mellitus with ophthalmic complication
C108111	Type I diabetes mellitus with ophthalmic complication
C108112	Type 1 diabetes mellitus with ophthalmic complication
C108200	Insulin-dependent diabetes mellitus with neurological
C108211	Type I diabetes mellitus with neurological complication
C108212	Type 1 diabetes mellitus with neurological complication
C108300	Insulin dependent diabetes mellitus with multiple com
C108311	Type I diabetes mellitus with multiple complications
C108312	Type 1 diabetes mellitus with multiple complications
C108400	Unstable insulin dependent diabetes mellitus
C108411	Unstable type I diabetes mellitus
C108412	Unstable type 1 diabetes mellitus
C108500	Insulin dependent diabetes mellitus with ulcer
C108511	Type I diabetes mellitus with ulcer
C108512	Type 1 diabetes mellitus with ulcer
C108600	Insulin dependent diabetes mellitus with gangrene
C108611	Type I diabetes mellitus with gangrene
C108612	Type 1 diabetes mellitus with gangrene

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Read code	Description
C108700	Insulin dependent diabetes mellitus with retinopathy
C108711	Type I diabetes mellitus with retinopathy
C108712	Type 1 diabetes mellitus with retinopathy
C108800	Insulin dependent diabetes mellitus - poor control
C108811	Type I diabetes mellitus - poor control
C108812	Type 1 diabetes mellitus - poor control
C108900	Insulin dependent diabetes maturity onset
C108911	Type I diabetes mellitus maturity onset
C108912	Type 1 diabetes mellitus maturity onset
C108A00	Insulin-dependent diabetes without complication
C108A11	Type I diabetes mellitus without complication
C108A12	Type 1 diabetes mellitus without complication
C108B00	Insulin dependent diabetes mellitus with mononeuropathy
C108B11	Type I diabetes mellitus with mononeuropathy
C108B12	Type 1 diabetes mellitus with mononeuropathy
C108C00	Insulin dependent diabetes mellitus with polyneuropathy
C108C11	Type I diabetes mellitus with polyneuropathy
C108C12	Type 1 diabetes mellitus with polyneuropathy
C108D00	Insulin dependent diabetes mellitus with nephropathy
C108D11	Type I diabetes mellitus with nephropathy
C108D12	Type 1 diabetes mellitus with nephropathy
C108E00	Insulin dependent diabetes mellitus with hypoglycaemic
C108E11	Type I diabetes mellitus with hypoglycaemic coma
C108E12	Type 1 diabetes mellitus with hypoglycaemic coma
C108F00	Insulin dependent diabetes mellitus with diabetic cataract
C108F11	Type I diabetes mellitus with diabetic cataract
C108F12	Type 1 diabetes mellitus with diabetic cataract
C108G00	Insulin dependent diabetes mellitus with peripheral angiopathy
C108G11	Type I diabetes mellitus with peripheral angiopathy
C108G12	Type 1 diabetes mellitus with peripheral angiopathy
C108H00	Insulin dependent diabetes mellitus with arthropathy
C108H11	Type I diabetes mellitus with arthropathy
C108H12	Type 1 diabetes mellitus with arthropathy
C108J00	Insulin dependent diabetes mellitus with neuropathic arthropathy
C108J11	Type I diabetes mellitus with neuropathic arthropathy
C108J12	Type 1 diabetes mellitus with neuropathic arthropathy
C108y00	Other specified diabetes mellitus with multiple comps
C108z00	Unspecified diabetes mellitus with multiple complication
C109.00	Non-insulin dependent diabetes mellitus
C109.11	NIDDM - Non-insulin dependent diabetes mellitus
C109.12	Type 2 diabetes mellitus
C109.13	Type II diabetes mellitus
C109000	Non-insulin-dependent diabetes mellitus with renal co
C109011	Type II diabetes mellitus with renal complications

Continued on next page

Read code	Description
C109012	Type 2 diabetes mellitus with renal complications
C109100	Non-insulin-dependent diabetes mellitus with ophthalmic
C109111	Type II diabetes mellitus with ophthalmic complication
C109112	Type 2 diabetes mellitus with ophthalmic complication
C109200	Non-insulin-dependent diabetes mellitus with neuro co
C109211	Type II diabetes mellitus with neurological complication
C109212	Type 2 diabetes mellitus with neurological complication
C109300	Non-insulin-dependent diabetes mellitus with multiple
C109311	Type II diabetes mellitus with multiple complications
C109312	Type 2 diabetes mellitus with multiple complications
C109400	Non-insulin dependent diabetes mellitus with ulcer
C109411	Type II diabetes mellitus with ulcer
C109412	Type 2 diabetes mellitus with ulcer
C109500	Non-insulin dependent diabetes mellitus with gangrene
C109511	Type II diabetes mellitus with gangrene
C109512	Type 2 diabetes mellitus with gangrene
C109600	Non-insulin-dependent diabetes mellitus with retinopathy
C109611	Type II diabetes mellitus with retinopathy
C109612	Type 2 diabetes mellitus with retinopathy
C109700	Non-insulin dependent diabetes mellitus - poor control
C109711	Type II diabetes mellitus - poor control
C109712	Type 2 diabetes mellitus - poor control
C109900	Non-insulin-dependent diabetes mellitus without complications
C109911	Type II diabetes mellitus without complication
C109912	Type 2 diabetes mellitus without complication
C109A00	Non-insulin dependent diabetes mellitus with mononeuropathy
C109A11	Type II diabetes mellitus with mononeuropathy
C109A12	Type 2 diabetes mellitus with mononeuropathy
C109B00	Non-insulin dependent diabetes mellitus with polyneuropathy
C109B11	Type II diabetes mellitus with polyneuropathy
C109B12	Type 2 diabetes mellitus with polyneuropathy
C109C00	Non-insulin dependent diabetes mellitus with nephropathy
C109C11	Type II diabetes mellitus with nephropathy
C109C12	Type 2 diabetes mellitus with nephropathy
C109D00	Non-insulin dependent diabetes mellitus with hypoglycaemic
C109D11	Type II diabetes mellitus with hypoglycaemic coma
C109D12	Type 2 diabetes mellitus with hypoglycaemic coma
C109E00	Non-insulin depend diabetes mellitus with diabetic cataract
C109E11	Type II diabetes mellitus with diabetic cataract
C109E12	Type 2 diabetes mellitus with diabetic cataract
C109F00	Non-insulin-dependent d m with peripheral angiopathy
C109F11	Type II diabetes mellitus with peripheral angiopathy
C109F12	Type 2 diabetes mellitus with peripheral angiopathy
C109G00	Non-insulin dependent diabetes mellitus with arthropathy

Continued on next page

Read code	Description
C109G11	Type II diabetes mellitus with arthropathy
C109G12	Type 2 diabetes mellitus with arthropathy
C109H00	Non-insulin dependent d m with neuropathic arthropathy
C109H11	Type II diabetes mellitus with neuropathic arthropathy
C109H12	Type 2 diabetes mellitus with neuropathic arthropathy
C109J00	Insulin treated Type 2 diabetes mellitus
C109J11	Insulin treated non-insulin dependent diabetes mellitus
C109J12	Insulin treated Type II diabetes mellitus
C109K00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10A.00	Malnutrition-related diabetes mellitus
C10A000	Malnutrition-related diabetes mellitus with coma
C10A100	Malnutrition-related diabetes mellitus with ketoacidosis
C10A200	Malnutrition-related diabetes mellitus with renal complication
C10A300	Malnutrit-related diabetes mellitus with ophthalmic complication
C10A400	Malnutrition-related diabetes mellitus with neuro complication
C10A500	Malnutritn-relat diabetes mellitus with peripheral circulation compilation
C10A600	Malnutrition-related diabetes mellitus with multiple
C10A700	Malnutrition-related diabetes mellitus without complication
C10AW00	Malnutrit-related diabetes mellitus with unspecific complication
C10AX00	Malnutrit-related diabetes mellitus with other spec complication
C10B.00	Diabetes mellitus induced by steroids
C10B000	Steroid induced diabetes mellitus without complication
C10C.00	Diabetes mellitus autosomal dominant
C10D.00	Diabetes mellitus autosomal dominant type 2
C10D.11	Maturity onset diabetes in youth type 2
C10E.00	Type 1 diabetes mellitus
C10E.11	Type I diabetes mellitus
C10E.12	Insulin dependent diabetes mellitus
C10E000	Type 1 diabetes mellitus with renal complications
C10E011	Type I diabetes mellitus with renal complications
C10E012	Insulin-dependent diabetes mellitus with renal complication
C10E100	Type 1 diabetes mellitus with ophthalmic complication
C10E111	Type I diabetes mellitus with ophthalmic complication
C10E112	Insulin-dependent diabetes mellitus with ophthalmic complication
C10E200	Type 1 diabetes mellitus with neurological complication
C10E211	Type I diabetes mellitus with neurological complication
C10E212	Insulin-dependent diabetes mellitus with neurological
C10E300	Type 1 diabetes mellitus with multiple complications
C10E311	Type I diabetes mellitus with multiple complications
C10E312	Insulin dependent diabetes mellitus with multiple com
C10E400	Unstable type 1 diabetes mellitus
C10E411	Unstable type I diabetes mellitus
C10E412	Unstable insulin dependent diabetes mellitus
C10E500	Type 1 diabetes mellitus with ulcer

Continued on next page

Read code	Description
C10E511	Type I diabetes mellitus with ulcer
C10E512	Insulin dependent diabetes mellitus with ulcer
C10E600	Type 1 diabetes mellitus with gangrene
C10E611	Type I diabetes mellitus with gangrene
C10E612	Insulin dependent diabetes mellitus with gangrene
C10E700	Type 1 diabetes mellitus with retinopathy
C10E711	Type I diabetes mellitus with retinopathy
C10E712	Insulin dependent diabetes mellitus with retinopathy
C10E800	Type 1 diabetes mellitus - poor control
C10E811	Type I diabetes mellitus - poor control
C10E812	Insulin dependent diabetes mellitus - poor control
C10E900	Type 1 diabetes mellitus maturity onset
C10E911	Type I diabetes mellitus maturity onset
C10E912	Insulin dependent diabetes maturity onset
C10EA00	Type 1 diabetes mellitus without complication
C10EA11	Type I diabetes mellitus without complication
C10EA12	Insulin-dependent diabetes without complication
C10EB00	Type 1 diabetes mellitus with mononeuropathy
C10EB11	Type I diabetes mellitus with mononeuropathy
C10EB12	Insulin dependent diabetes mellitus with mononeuropathy
C10EC00	Type 1 diabetes mellitus with polyneuropathy
C10EC11	Type I diabetes mellitus with polyneuropathy
C10EC12	Insulin dependent diabetes mellitus with polyneuropathy
C10ED00	Type 1 diabetes mellitus with nephropathy
C10ED11	Type I diabetes mellitus with nephropathy
C10ED12	Insulin dependent diabetes mellitus with nephropathy
C10EE00	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE11	Type I diabetes mellitus with hypoglycaemic coma
C10EE12	Insulin dependent diabetes mellitus with hypoglycaemia
C10EF00	Type 1 diabetes mellitus with diabetic cataract
C10EF11	Type I diabetes mellitus with diabetic cataract
C10EF12	Insulin dependent diabetes mellitus with diabetic cat
C10EG00	Type 1 diabetes mellitus with peripheral angiopathy
C10EG11	Type I diabetes mellitus with peripheral angiopathy
C10EG12	Insulin dependent diabetes mellitus with peripheral angiopathy
C10EH00	Type 1 diabetes mellitus with arthropathy
C10EH11	Type I diabetes mellitus with arthropathy
C10EH12	Insulin dependent diabetes mellitus with arthropathy
C10EJ00	Type 1 diabetes mellitus with neuropathic arthropathy
C10EJ11	Type I diabetes mellitus with neuropathic arthropathy
C10EJ12	Insulin dependent diabetes mellitus with neuropathic arthropathy
C10EK00	Type 1 diabetes mellitus with persistent proteinuria
C10EK11	Type I diabetes mellitus with persistent proteinuria
C10EL00	Type 1 diabetes mellitus with persistent microalbumin

Continued on next page

Read code	Description
C10EL11	Type I diabetes mellitus with persistent microalbumin
C10EM00	Type 1 diabetes mellitus with ketoacidosis
C10EM11	Type I diabetes mellitus with ketoacidosis
C10EN00	Type 1 diabetes mellitus with ketoacidotic coma
C10EN11	Type I diabetes mellitus with ketoacidotic coma
C10EP00	Type 1 diabetes mellitus with exudative maculopathy
C10EP11	Type I diabetes mellitus with exudative maculopathy
C10EQ00	Type 1 diabetes mellitus with gastroparesis
C10EQ11	Type I diabetes mellitus with gastroparesis
C10F.00	Type 2 diabetes mellitus
C10F.11	Type II diabetes mellitus
C10F000	Type 2 diabetes mellitus with renal complications
C10F011	Type II diabetes mellitus with renal complications
C10F100	Type 2 diabetes mellitus with ophthalmic complication
C10F111	Type II diabetes mellitus with ophthalmic complication
C10F200	Type 2 diabetes mellitus with neurological complication
C10F211	Type II diabetes mellitus with neurological complication
C10F300	Type 2 diabetes mellitus with multiple complications
C10F311	Type II diabetes mellitus with multiple complications
C10F400	Type 2 diabetes mellitus with ulcer
C10F411	Type II diabetes mellitus with ulcer
C10F500	Type 2 diabetes mellitus with gangrene
C10F511	Type II diabetes mellitus with gangrene
C10F600	Type 2 diabetes mellitus with retinopathy
C10F611	Type II diabetes mellitus with retinopathy
C10F700	Type 2 diabetes mellitus - poor control
C10F711	Type II diabetes mellitus - poor control
C10F900	Type 2 diabetes mellitus without complication
C10F911	Type II diabetes mellitus without complication
C10FA00	Type 2 diabetes mellitus with mononeuropathy
C10FA11	Type II diabetes mellitus with mononeuropathy
C10FB00	Type 2 diabetes mellitus with polyneuropathy
C10FB11	Type II diabetes mellitus with polyneuropathy
C10FC00	Type 2 diabetes mellitus with nephropathy
C10FC11	Type II diabetes mellitus with nephropathy
C10FD00	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD11	Type II diabetes mellitus with hypoglycaemic coma
C10FE00	Type 2 diabetes mellitus with diabetic cataract
C10FE11	Type II diabetes mellitus with diabetic cataract
C10FF00	Type 2 diabetes mellitus with peripheral angiopathy
C10FF11	Type II diabetes mellitus with peripheral angiopathy
C10FG00	Type 2 diabetes mellitus with arthropathy
C10FG11	Type II diabetes mellitus with arthropathy
C10FH00	Type 2 diabetes mellitus with neuropathic arthropathy

Continued on next page

Read code	Description
C10FH11	Type II diabetes mellitus with neuropathic arthropathy
C10FJ00	Insulin treated Type 2 diabetes mellitus
C10FJ11	Insulin treated Type II diabetes mellitus
C10FK00	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FK11	Hyperosmolar non-ketotic state in type II diabetes me
C10FL00	Type 2 diabetes mellitus with persistent proteinuria
C10FL11	Type II diabetes mellitus with persistent proteinuria
C10FM00	Type 2 diabetes mellitus with persistent microalbumin
C10FM11	Type II diabetes mellitus with persistent microalbumi
C10FN00	Type 2 diabetes mellitus with ketoacidosis
C10FN11	Type II diabetes mellitus with ketoacidosis
C10FP00	Type 2 diabetes mellitus with ketoacidotic coma
C10FP11	Type II diabetes mellitus with ketoacidotic coma
C10FQ00	Type 2 diabetes mellitus with exudative maculopathy
C10FQ11	Type II diabetes mellitus with exudative maculopathy
C10FR00	Type 2 diabetes mellitus with gastroparesis
C10FR11	Type II diabetes mellitus with gastroparesis
C10FS00	Maternally inherited diabetes mellitus
C10G.00	Secondary pancreatic diabetes mellitus
C10G000	Secondary pancreatic diabetes mellitus without complication
C10H.00	Diabetes mellitus induced by non-steroid drugs
C10H000	DM induced by non-steroid drugs without complication
C10J.00	Insulin autoimmune syndrome
C10J000	Insulin autoimmune syndrome without complication
C10K.00	Type A insulin resistance
C10K000	Type A insulin resistance without complication
C10M.00	Lipoatrophic diabetes mellitus
C10M000	Lipoatrophic diabetes mellitus without complication
C10N100	Cystic fibrosis related diabetes mellitus
C10y.00	Diabetes mellitus with other specified manifestation
C10y000	Diabetes mellitus, juvenile, + other specified manifestation
C10y100	Diabetes mellitus, adult, + other specified manifestation
C10yy00	Other specified diabetes mellitus with other spec com
C10yz00	Diabetes mellitus NOS with other specified manifestation
C10z.00	Diabetes mellitus with unspecified complication
C10z000	Diabetes mellitus, juvenile type, + unspecified complication
C10z100	Diabetes mellitus, adult onset, + unspecified complication
C10zy00	Other specified diabetes mellitus with unspecified complications
C10zz00	Diabetes mellitus NOS with unspecified complication
Cyu2.00	[X]Diabetes mellitus
Cyu2000	[X]Other specified diabetes mellitus
Cyu2100	[X]Malnutrit-relat diabetes mellitus with other spec
Cyu2200	[X]Malnutrit-related diabetes mellitus with unspecified complications
Cyu2300	[X]Unspecified diabetes mellitus with renal complications

Continued on next page

Read code	Description
F171100	Autonomic neuropathy due to diabetes
F345000	Diabetic mononeuritis multiplex
F35z000	Diabetic mononeuritis NOS
F372.00	Polyneuropathy in diabetes
F372.11	Diabetic polyneuropathy
F372.12	Diabetic neuropathy
F372000	Acute painful diabetic neuropathy
F372100	Chronic painful diabetic neuropathy
F372200	Asymptomatic diabetic neuropathy
F381300	Myasthenic syndrome due to diabetic amyotrophy
F381311	Diabetic amyotrophy
F3y0.00	Diabetic mononeuropathy
F420.00	Diabetic retinopathy
F420000	Background diabetic retinopathy
F420100	Proliferative diabetic retinopathy
F420200	Preproliferative diabetic retinopathy
F420300	Advanced diabetic maculopathy
F420400	Diabetic maculopathy
F420500	Advanced diabetic retinal disease
F420600	Non proliferative diabetic retinopathy
F420700	High risk proliferative diabetic retinopathy
F420800	High risk non proliferative diabetic retinopathy
F420z00	Diabetic retinopathy NOS
F440700	Diabetic iritis
F464000	Diabetic cataract
G73y000	Diabetic peripheral angiopathy
K01x100	Nephrotic syndrome in diabetes mellitus
K08yA00	Proteinuric diabetic nephropathy
K08yA11	Clinical diabetic nephropathy
Kyu0300	[X]Glomerular disorders in diabetes mellitus
L180000	Diabetes mellitus - unspecific whether in pregnancy/puerperium
L180200	Diabetes mellitus in puerperium - baby delivered
L180300	Diabetes mellitus during pregnancy - baby not yet delivered
L180400	Diabetes mellitus in puerperium - baby previously delivered
L180500	Pre-existing diabetes mellitus, insulin-dependent
L180600	Pre-existing diabetes mellitus, non-insulin-dependent
L180700	Pre-existing malnutrition-related diabetes mellitus
L180X00	Pre-existing diabetes mellitus, unspecified
Lyu2900	[X]Pre-existing diabetes mellitus, unspecified
M037200	Cellulitis in diabetic foot
M271000	Ischaemic ulcer diabetic foot
M271100	Neuropathic diabetic ulcer - foot
M271200	Mixed diabetic ulcer - foot
N030000	Diabetic cheiroarthropathy

Continued on next page

Read code	Description
N030011	Diabetic cheiropathy
N030100	Diabetic Charcot arthropathy
Q441.00	Neonatal diabetes mellitus
R054200	[D]Gangrene of toe in diabetic
R054300	[D]Widespread diabetic foot gangrene
SL23z00	Insulins or antidiabetic poisoning NOS
TJ23.00	Adverse reaction to insulins and antidiabetic agents
TJ23z00	Adverse reaction to insulins and antidiabetic agents
U602311	[X] Adverse reaction to insulins and antidiabetic age
U60231E	[X] Adverse reaction to insulins and antidiabetic age
ZC2C800	Dietary advice for diabetes mellitus
ZC2C900	Dietary advice for type I diabetes
ZC2C911	Diet advice for insulin-dependent diabetes
ZC2CA00	Dietary advice for type II diabetes
ZC2CA11	Dietary advice non-insulin-dependent diabetes
ZL22500	Under care of diabetic liaison nurse
ZL62500	Referral to diabetes nurse
ZL62600	Referral to diabetic liaison nurse
ZLA2500	Seen by diabetic liaison nurse
ZLD7500	Discharge by diabetic liaison nurse
ZRB4.00	Diabetes clinic satisfaction questionnaire
ZRB4.11	CSQ - Diabetes clinic satisfaction questionnaire
ZRB5.00	Diabetes treatment satisfaction questionnaire
ZRB5.11	DTSQ - Diabetes treatment satisfaction questionnaire
ZRB6.00	Diabetes wellbeing questionnaire
ZRB6.11	DWBQ - Diabetes wellbeing questionnaire
ZRBa.00	Education score - diabetes
ZRbH.00	Perceived control of insulin-dependent diabetes
ZV65312	[V]Dietary counselling in diabetes mellitus

9.9 Therapy codes for identifying diabetes mellitus

Therapy code	Diabetes drug type
60064979	Insulin
81164998	Insulin
81426998	Insulin
81687998	Insulin
81790998	Insulin
81962998	Insulin
81963998	Insulin
82457998	Insulin
82458998	Insulin
83403998	Insulin
83404998	Insulin
83405998	Insulin
84421998	Insulin
84422998	Insulin
84779998	Insulin
85591998	Insulin
86028998	Insulin
86029998	Insulin
86044998	Insulin
86045998	Insulin
86046998	Insulin
86047998	Insulin
86077998	Insulin
86078998	Insulin
86080998	Insulin
86081998	Insulin
86168998	Insulin
86169998	Insulin
86173998	Insulin
86174998	Insulin
86175998	Insulin
86176998	Insulin
86177998	Insulin
86178998	Insulin
86179998	Insulin
86180998	Insulin
86182998	Insulin
86183998	Insulin
86184998	Insulin
86185998	Insulin
86186998	Insulin

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Therapy code	Diabetes drug type
86187998	Insulin
86188998	Insulin
86189998	Insulin
86190998	Insulin
86191998	Insulin
86193998	Insulin
86194998	Insulin
86214998	Insulin
86215998	Insulin
86236998	Insulin
86237998	Insulin
86238998	Insulin
86239998	Insulin
86240998	Insulin
86241998	Insulin
86242998	Insulin
86243998	Insulin
86245998	Insulin
86246998	Insulin
86247998	Insulin
86248998	Insulin
86249998	Insulin
86250998	Insulin
86251998	Insulin
86252998	Insulin
86253998	Insulin
86254998	Insulin
86255998	Insulin
86256998	Insulin
86259998	Insulin
86260998	Insulin
86261998	Insulin
86262998	Insulin
86263998	Insulin
86264998	Insulin
86265998	Insulin
86266998	Insulin
86267998	Insulin
86268998	Insulin
86269998	Insulin
86270998	Insulin
86271998	Insulin
86272998	Insulin
86274998	Insulin

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Therapy code	Diabetes drug type
86275998	Insulin
86276998	Insulin
86278998	Insulin
86279998	Insulin
86280998	Insulin
86281998	Insulin
86282998	Insulin
86283998	Insulin
86284998	Insulin
86286998	Insulin
86287998	Insulin
86288998	Insulin
86291998	Insulin
86294998	Insulin
86295998	Insulin
86298998	Insulin
86300998	Insulin
86301998	Insulin
86303998	Insulin
86304998	Insulin
86305998	Insulin
86306998	Insulin
86308998	Insulin
86309998	Insulin
86310998	Insulin
86311998	Insulin
86312998	Insulin
86313998	Insulin
86314998	Insulin
86315998	Insulin
86316998	Insulin
86317998	Insulin
86318998	Insulin
86319998	Insulin
86549998	Insulin
86551998	Insulin
86553998	Insulin
87365979	Insulin
87373979	Insulin
87385979	Insulin
87411979	Insulin
87416979	Insulin
87434979	Insulin
87435979	Insulin

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Therapy code	Diabetes drug type
87442979	Insulin
87471998	Insulin
87472998	Insulin
87473998	Insulin
87967998	Insulin
88003998	Insulin
88413998	Insulin
88851998	Insulin
88978998	Insulin
88995998	Insulin
88999998	Insulin
89554998	Insulin
89555998	Insulin
89640979	Insulin
89668979	Insulin
89888998	Insulin
89990997	Insulin
89990998	Insulin
90012998	Insulin
90015998	Insulin
90168998	Insulin
90169998	Insulin
90202979	Insulin
90379998	Insulin
90682997	Insulin
90682998	Insulin
90683997	Insulin
90683998	Insulin
90684996	Insulin
90684997	Insulin
90684998	Insulin
90685998	Insulin
90686998	Insulin
90687998	Insulin
90688998	Insulin
90689998	Insulin
90690998	Insulin
90691998	Insulin
90697996	Insulin
90697997	Insulin
90697998	Insulin
90698998	Insulin
91273997	Insulin
91273998	Insulin

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Therapy code	Diabetes drug type
91274998	Insulin
91275996	Insulin
91275997	Insulin
91275998	Insulin
91276998	Insulin
91289998	Insulin
91290996	Insulin
91290997	Insulin
91290998	Insulin
91291997	Insulin
91291998	Insulin
91292996	Insulin
91292997	Insulin
91292998	Insulin
91293997	Insulin
91293998	Insulin
91294997	Insulin
91294998	Insulin
91295998	Insulin
91505998	Insulin
91509998	Insulin
91612998	Insulin
91700998	Insulin
91701998	Insulin
91758998	Insulin
92323998	Insulin
92376996	Insulin
92376997	Insulin
92555998	Insulin
92906998	Insulin
92907998	Insulin
92908998	Insulin
92909998	Insulin
92932998	Insulin
93137992	Insulin
93139992	Insulin
93467992	Insulin
93572979	Insulin
94201992	Insulin
94202992	Insulin
94292998	Insulin
94298998	Insulin
94319998	Insulin
94322998	Insulin

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Therapy code	Diabetes drug type
94328998	Insulin
94337998	Insulin
94413998	Insulin
94436998	Insulin
94477992	Insulin
94948998	Insulin
95158992	Insulin
95162992	Insulin
95163992	Insulin
95164992	Insulin
95168992	Insulin
95846992	Insulin
96044992	Insulin
96045998	Insulin
96046992	Insulin
96046998	Insulin
96047998	Insulin
96048998	Insulin
96049998	Insulin
96050998	Insulin
96051998	Insulin
96053997	Insulin
96055998	Insulin
96056998	Insulin
96057998	Insulin
96058998	Insulin
96060998	Insulin
96061998	Insulin
96062998	Insulin
96064992	Insulin
96065998	Insulin
96076992	Insulin
96282992	Insulin
96283992	Insulin
96284992	Insulin
96285992	Insulin
96286992	Insulin
96287992	Insulin
96289992	Insulin
96290992	Insulin
96291992	Insulin
96292992	Insulin
96294992	Insulin
96295992	Insulin

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Therapy code	Diabetes drug type
96548992	Insulin
96688992	Insulin
96689992	Insulin
96787992	Insulin
96792992	Insulin
96794992	Insulin
96795992	Insulin
97051997	Insulin
97051998	Insulin
97052996	Insulin
97052997	Insulin
97052998	Insulin
97053998	Insulin
97244992	Insulin
97322997	Insulin
97322998	Insulin
97323998	Insulin
97525998	Insulin
97526998	Insulin
97527998	Insulin
97528998	Insulin
97599992	Insulin
97600992	Insulin
97602992	Insulin
97854998	Insulin
98048990	Insulin
98198998	Insulin
98225998	Insulin
98226998	Insulin
98227998	Insulin
98228996	Insulin
98228997	Insulin
98228998	Insulin
98268998	Insulin
98474990	Insulin
98480998	Insulin
98481997	Insulin
98481998	Insulin
98505998	Insulin
98525990	Insulin
98817998	Insulin
98895998	Insulin
98982998	Insulin
99144998	Insulin

Continued on next page

Therapy code	Diabetes drug type
99196998	Insulin
99401998	Insulin
99402998	Insulin
99415998	Insulin
99480998	Insulin
99532998	Insulin
99533998	Insulin
99553998	Insulin
99554998	Insulin
99556998	Insulin
99557998	Insulin
99976992	Insulin
99977992	Insulin
99978992	Insulin
54786979	Metformin
58558979	Metformin
79510979	Metformin
81158998	Metformin
81344998	Metformin
81701998	Metformin
82916998	Metformin
82917998	Metformin
82918998	Metformin
82919998	Metformin
83031998	Metformin
83032998	Metformin
83619998	Metformin
83732998	Metformin
83733998	Metformin
85555998	Metformin
85673998	Metformin
85674998	Metformin
87053998	Metformin
87054998	Metformin
87536998	Metformin
87883998	Metformin
89129979	Metformin
89868979	Metformin
89870979	Metformin
91221997	Metformin
91221998	Metformin
92983990	Metformin
93167990	Metformin
94235992	Metformin

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Therapy code	Diabetes drug type
94248990	Metformin
95270992	Metformin
95271992	Metformin
95272992	Metformin
95600990	Metformin
95880998	Metformin
96111990	Metformin
96270990	Metformin
96850990	Metformin
97087997	Metformin
97087998	Metformin
97110989	Metformin
97110990	Metformin
98125989	Metformin
98125990	Metformin
98493989	Metformin
98493990	Metformin
98654989	Metformin
98654990	Metformin
99149990	Metformin
99513989	Metformin
99513990	Metformin
99514989	Metformin
99514990	Metformin
99590997	Metformin
99590998	Metformin
53325979	Other antidiabetic
53326979	Other antidiabetic
53327979	Other antidiabetic
53328979	Other antidiabetic
54904979	Other antidiabetic
54905979	Other antidiabetic
54906979	Other antidiabetic
54907979	Other antidiabetic
59371979	Other antidiabetic
59372979	Other antidiabetic
59373979	Other antidiabetic
59374979	Other antidiabetic
81159998	Other antidiabetic
81160998	Other antidiabetic
81305998	Other antidiabetic
81307998	Other antidiabetic
81513998	Other antidiabetic
81514998	Other antidiabetic

Continued on next page

Therapy code	Diabetes drug type
82068998	Other antidiabetic
82573998	Other antidiabetic
82575998	Other antidiabetic
82793998	Other antidiabetic
82794998	Other antidiabetic
83401998	Other antidiabetic
84008998	Other antidiabetic
84009998	Other antidiabetic
84010998	Other antidiabetic
84011998	Other antidiabetic
84338998	Other antidiabetic
84341998	Other antidiabetic
84639998	Other antidiabetic
84640998	Other antidiabetic
84693998	Other antidiabetic
84694998	Other antidiabetic
84696998	Other antidiabetic
84697998	Other antidiabetic
85266998	Other antidiabetic
85267998	Other antidiabetic
85268998	Other antidiabetic
85622998	Other antidiabetic
85624998	Other antidiabetic
85625998	Other antidiabetic
87165998	Other antidiabetic
87166998	Other antidiabetic
87179998	Other antidiabetic
87180998	Other antidiabetic
87181998	Other antidiabetic
87182998	Other antidiabetic
87770998	Other antidiabetic
87771998	Other antidiabetic
87772998	Other antidiabetic
87773998	Other antidiabetic
87774998	Other antidiabetic
87775998	Other antidiabetic
87884998	Other antidiabetic
87885998	Other antidiabetic
88131996	Other antidiabetic
88131997	Other antidiabetic
88131998	Other antidiabetic
88132996	Other antidiabetic
88132997	Other antidiabetic
88132998	Other antidiabetic

Continued on next page

Therapy code	Diabetes drug type
88523996	Other antidiabetic
88523998	Other antidiabetic
88528996	Other antidiabetic
88528998	Other antidiabetic
89763996	Other antidiabetic
89763997	Other antidiabetic
90048996	Other antidiabetic
90048997	Other antidiabetic
90048998	Other antidiabetic
91908990	Other antidiabetic
91923996	Other antidiabetic
91923997	Other antidiabetic
91923998	Other antidiabetic
91924996	Other antidiabetic
91924997	Other antidiabetic
91924998	Other antidiabetic
92237997	Other antidiabetic
92237998	Other antidiabetic
92238997	Other antidiabetic
92238998	Other antidiabetic
92999979	Other antidiabetic
94470992	Other antidiabetic
96051992	Other antidiabetic
96252998	Other antidiabetic
96253996	Other antidiabetic
96253997	Other antidiabetic
96253998	Other antidiabetic
96264998	Other antidiabetic
98475997	Other antidiabetic
98475998	Other antidiabetic
98803998	Other antidiabetic
98915997	Other antidiabetic
98915998	Other antidiabetic
81260998	Sulphonylureas
82136998	Sulphonylureas
82137998	Sulphonylureas
82304998	Sulphonylureas
82989998	Sulphonylureas
83916998	Sulphonylureas
83949998	Sulphonylureas
85901998	Sulphonylureas
86018998	Sulphonylureas
88135998	Sulphonylureas
88334998	Sulphonylureas

Continued on next page

Therapy code	Diabetes drug type
88355998	Sulphonylureas
88447996	Sulphonylureas
88447997	Sulphonylureas
88447998	Sulphonylureas
88449996	Sulphonylureas
88449997	Sulphonylureas
88449998	Sulphonylureas
91407998	Sulphonylureas
91559998	Sulphonylureas
92831990	Sulphonylureas
93545979	Sulphonylureas
94371992	Sulphonylureas
95025990	Sulphonylureas
95149997	Sulphonylureas
95149998	Sulphonylureas
95150997	Sulphonylureas
95150998	Sulphonylureas
95672992	Sulphonylureas
95674992	Sulphonylureas
95870992	Sulphonylureas
95898990	Sulphonylureas
96220990	Sulphonylureas
96280998	Sulphonylureas
96281998	Sulphonylureas
96282997	Sulphonylureas
96282998	Sulphonylureas
96283997	Sulphonylureas
96283998	Sulphonylureas
96427990	Sulphonylureas
96495990	Sulphonylureas
96687998	Sulphonylureas
96755997	Sulphonylureas
96755998	Sulphonylureas
96893990	Sulphonylureas
96981998	Sulphonylureas
97026990	Sulphonylureas
97032990	Sulphonylureas
97057997	Sulphonylureas
97057998	Sulphonylureas
97089998	Sulphonylureas
97097997	Sulphonylureas
97109998	Sulphonylureas
97127997	Sulphonylureas
97127998	Sulphonylureas

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Therapy code	Diabetes drug type
97133992	Sulphonylureas
97146990	Sulphonylureas
97166990	Sulphonylureas
97202990	Sulphonylureas
97236992	Sulphonylureas
97303998	Sulphonylureas
97537997	Sulphonylureas
97537998	Sulphonylureas
97538990	Sulphonylureas
97552990	Sulphonylureas
97583997	Sulphonylureas
97583998	Sulphonylureas
97590990	Sulphonylureas
97834990	Sulphonylureas
97889990	Sulphonylureas
97938990	Sulphonylureas
98053990	Sulphonylureas
98133990	Sulphonylureas
98188989	Sulphonylureas
98664989	Sulphonylureas
98664990	Sulphonylureas
99145998	Sulphonylureas
99195998	Sulphonylureas
99246990	Sulphonylureas
99347990	Sulphonylureas
99349990	Sulphonylureas
99419998	Sulphonylureas
99580989	Sulphonylureas
99580990	Sulphonylureas
99582989	Sulphonylureas
99582990	Sulphonylureas
99588998	Sulphonylureas
99589998	Sulphonylureas
99591998	Sulphonylureas
99668997	Sulphonylureas
99668998	Sulphonylureas
99754998	Sulphonylureas
99764997	Sulphonylureas
99764998	Sulphonylureas
99787998	Sulphonylureas

9.10 Additional health data codes to identify diabetes mellitus

AHD code	Description
1001400140	Hb A1C - Diabetic control
1001400327	Diabetic retinopathy screening
1009100000	Diabetes annual check
1009111000	Diabetes current status
1009120000	Diabetes insulin dosage

Appendix III. Outcome code lists

9.11 Read code list to identify for caesarean section delivery

Read code	Description
14Y0.00	Born by caesarean section
14Y2.00	Born by elective caesarean section
14Y6.00	Born by emergency caesarean section
7F12.00	Elective caesarean delivery
7F12000	Elective upper uterine segment caesarean delivery
7F12100	Elective lower uterine segment caesarean delivery
7F12111	Elective lower uterine segment caesarean section (LSC
7F12y00	Other specified elective caesarean delivery
7F12z00	Elective caesarean delivery NOS
7F13.00	Other caesarean delivery
7F13000	Upper uterine segment caesarean delivery NEC
7F13100	Lower uterine segment caesarean delivery NEC
7F13111	Lower uterine segment caesarean section (LSCS) NEC
7F13200	Extraperitoneal caesarean section
7F13300	Emergency caesarean section
7F13y00	Other specified other caesarean delivery
7F13z00	Other caesarean delivery NOS
L213200	Multiple delivery, all by caesarean section
L398.00	Caesarean delivery
L398000	Caesarean delivery unspecified
L398100	Caesarean delivery - delivered
L398200	Caesarean section - pregnancy at term
L398300	Delivery by elective caesarean section
L398400	Delivery by emergency caesarean section
L398500	Delivery by caesarean hysterectomy
L398600	Caesarean delivery following previous Caesarean delivery
L398z00	Caesarean delivery NOS
L441.00	Caesarean wound disruption
L441000	Caesarean wound disruption unspecified
L441100	Caesarean wound disruption - delivered with postnatal complication
L441200	Caesarean wound disruption with postnatal complication
L441z00	Caesarean wound disruption NOS
Lyu5200	[X]Other single delivery by caesarean section
Lyu6A00	[X]Infection of caesarean section wound following del
Q021300	Fetus/neonate affected by placental damage-caesarean
Q034.00	Fetus or neonate affected by caesarean section
Z254500	Delivered by caesarean section - pregnancy at term
Z254600	Delivered by caesarean following previous caesarean

9.12 Read code list to identify Instrumental delivery

Read code	Description
14Y5.00	Born by ventouse delivery
7F14.00	Breech extraction delivery
7F14000	Breech extraction delivery with version
7F14y00	Other specified breech extraction delivery
7F14z00	Breech extraction delivery NOS
7F17.00	Vacuum delivery
7F17.11	Ventouse delivery
7F17.12	Ventouse extraction
7F17000	High vacuum delivery
7F17100	Low vacuum delivery
7F17200	Vacuum delivery before full dilation of cervix
7F17y00	Other specified vacuum delivery
7F17z00	Vacuum delivery NOS
L213100	Multiple delivery, all by forceps and vacuum extraction
L395400	Delivery by combination of forceps and vacuum extract
L396.00	Vacuum extractor delivery
L396.11	Ventouse delivery
L396000	Vacuum extractor delivery unspecified
L396100	Vacuum extractor delivery - delivered
L396z00	Vacuum extractor delivery NOS
L397.00	Breech extraction
L397100	Breech extraction - delivered
L397z00	Breech extraction NOS
Q033.00	Fetus or neonate affected by vacuum extraction delivery
Q201200	Vacuum extraction chignon
Z254400	Deliveries by breech extraction
Z254700	Deliveries by vacuum extractor
14Y1.00	Born by forceps delivery
7F14100	Forceps to aftercoming head (breech)
7F15100	Assisted breech delivery
7F16.00	Forceps cephalic delivery
7F16000	High forceps cephalic delivery with rotation
7F16100	High forceps cephalic delivery NEC
7F16200	Mid forceps cephalic delivery with rotation
7F16300	Mid forceps cephalic delivery NEC
7F16400	Low forceps cephalic delivery
7F16500	Trial of forceps delivery
7F16900	Kielland forceps cephalic delivery with rotation
7F16y00	Other specified forceps cephalic delivery
7F16z00	Forceps cephalic delivery NOS
7F19000	Manually assisted vaginal delivery

Continued on next page

Read code	Description
L222.11	Assisted breech delivery
L395.00	Forceps delivery
L395.11	Keilland's forceps delivery
L395.12	Neville - Barnes forceps delivery
L395.13	Simpson's forceps delivery
L395000	Forceps delivery unspecified
L395100	Forceps delivery - delivered
L395200	Low forceps delivery
L395300	Mid-cavity forceps delivery
L395500	Mid-cavity forceps with rotation
L395z00	Forceps delivery NOS
Lyu5100	[X]Other and unspecified forceps delivery
Q032.00	Fetus or neonate affected by forceps delivery
Z254100	Deliveries by forceps - delivered
Z254200	Delivered by low forceps delivery
Z254300	Delivered by mid-cavity forceps delivery

9.13 Read code list to identify pregnancy induced hypertension, preeclampsia, and eclampsia

Read code	Description
246M.00	White coat hypertension
6146200	Hypertension induced by oral contraceptive pill
661M600	Hypertension self-management plan agreed
661N600	Hypertension self-management plan review
662..12	Hypertension monitoring
6627.00	Good hypertension control
6628.00	Poor hypertension control
6629.00	Hypertension: follow-up default
662F.00	Hypertension treatment started
662G.00	Hypertensive treatment changed
662H.00	Hypertension treatment stopped
662O.00	On treatment for hypertension
662P.00	Hypertension monitoring
662P000	Hypertension 9 month review
662b.00	Moderate hypertension control
662c.00	Hypertension six month review
662d.00	Hypertension annual review
662q.00	Trial reduction of antihypertensive therapy
662r.00	Trial withdrawal of antihypertensive therapy
7Q01.00	High cost hypertension drugs
7Q01y00	Other specified high cost hypertension drugs
7Q01z00	High cost hypertension drugs NOS
8B26.00	Antihypertensive therapy
8BL0.00	Patient on maximal tolerated antihypertensive therapy
8CR4.00	Hypertension clinical management plan
8HT5.00	Referral to hypertension clinic
8I3N.00	Hypertension treatment refused
8IA5.00	Trial withdrawal of antihypertensive therapy declined
8IA6.00	Trial reduction of antihypertensive therapy declined
9N03.00	Seen in hypertension clinic
9N1y200	Seen in hypertension clinic
9N4L.00	DNA - Did not attend hypertension clinic
9OI..00	Hypertension monitoring admin.
9OI..11	Hypertension clinic admin.
9OI1.00	Attends hypertension monitor.
9OI2.00	Refuses hypertension monitor.
9OI3.00	Hypertension monitor offer default
9OI4.00	Hypertension monitor.1st letter
9OI5.00	Hypertension monitor 2nd letter

Continued on next page

Read code	Description
9OI6.00	Hypertension monitor 3rd letter
9OI7.00	Hypertension monitor verbal inv.
9OI8.00	Hypertension monitor phone invite
9OI9.00	Hypertension monitor deleted
9OIA.00	Hypertension monitor check done
9OIA.11	Hypertension monitored
9OIZ.00	Hypertension monitoring admin NOS
9h3..00	Exception reporting: hypertension quality indicators
9h31.00	Excepted from hypertension quality indicators: Patient u
9h32.00	Excepted from hypertension quality indicators: Informed
G2...00	Hypertensive disease
G2...11	BP - hypertensive disease
G20..00	Essential hypertension
G20..11	High blood pressure
G20..12	Primary hypertension
G200.00	Malignant essential hypertension
G201.00	Benign essential hypertension
G202.00	Systolic hypertension
G203.00	Diastolic hypertension
G20z.00	Essential hypertension NOS
G20z.11	Hypertension NOS
G21..00	Hypertensive heart disease
G210.00	Malignant hypertensive heart disease
G210000	Malignant hypertensive heart disease without CCF
G210100	Malignant hypertensive heart disease with CCF
G210z00	Malignant hypertensive heart disease NOS
G211.00	Benign hypertensive heart disease
G211000	Benign hypertensive heart disease without CCF
G211100	Benign hypertensive heart disease with CCF
G211z00	Benign hypertensive heart disease NOS
G21z.00	Hypertensive heart disease NOS
G21z000	Hypertensive heart disease NOS without CCF
G21z011	Cardiomegaly - hypertensive
G21z100	Hypertensive heart disease NOS with CCF
G21zz00	Hypertensive heart disease NOS
G24..00	Secondary hypertension
G240.00	Secondary malignant hypertension
G240000	Secondary malignant renovascular hypertension
G240z00	Secondary malignant hypertension NOS
G241.00	Secondary benign hypertension
G241000	Secondary benign renovascular hypertension
G241z00	Secondary benign hypertension NOS
G244.00	Hypertension secondary to endocrine disorders
G24z.00	Secondary hypertension NOS

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Read code	Description
G24z000	Secondary renovascular hypertension NOS
G24z100	Hypertension secondary to drug
G24zz00	Secondary hypertension NOS
G25..00	Stage 1 hypertension (NICE - National Institute for Health Clinical Excellence
G25..11	Stage 1 hypertension
G26..00	Severe hypertension (Nat Inst for Health Clinical Ex
G26..11	Severe hypertension
G27..00	Hypertension resistant to drug therapy
G28..00	Stage 2 hypertension (NICE - National Institute for Health Clinical Excellence
G2y..00	Other specified hypertensive disease
G2z..00	Hypertensive disease NOS
G672.00	Hypertensive encephalopathy
G672.11	Hypertensive crisis
Gyu2.00	[X]Hypertensive diseases
Gyu2000	[X]Other secondary hypertension
L12..00	Hypertension complicating pregnancy/childbirth/puerperium
L120.00	Benign essential hypertension in pregnancy/childbirth/puerperium
L120000	Benign essential hypertension in pregnancy/childbirth/puerperium un
L120100	Benign essential hypertension in pregnancy/childbirth/puerperium -
L120200	Benign essential hypertension in pregnancy/childbirth/puerperium - delivery
L120300	Benign essential hypertension in pregnancy/childbirth/puerperium -no
L120400	Benign essential hypertension in pregnancy/childbirth/puerperium +p
L120z00	Benign essential hypertension in pregnancy/childbirth/puerperium NO
L122.00	Other pre-existing hypertension in pregnancy/childbirth/puerperium
L122000	Other pre-existing hypertension in pregnancy/childbirth/puerperium
L122100	Other pre-existing hypertension in pregnancy/childbirth/puerperium
L122300	Other pre-exist hypertension in pregnancy/childbirth/puerperium -not
L122400	Other pre-exist hypertension in pregnancy/childbirth/puerperium + p
L122z00	Other pre-existing hypertension in pregnancy/childbirth/puerperium
L123.00	Transient hypertension of pregnancy
L123000	Transient hypertension of pregnancy unspecified
L123100	Transient hypertension of pregnancy - delivered
L123200	Transient hypertension of pregnancy - delivery with p/n
L123300	Transient hypertension of pregnancy - not delivered
L123400	Transient hypertension of pregnancy + postnatal complication
L123500	Gestational hypertension
L123600	Transient hypertension of pregnancy
L123z00	Transient hypertension of pregnancy NOS
L124.00	Mild or unspecified pre-eclampsia
L124.11	Mild pre-eclampsia
L124.12	Toxaemia NOS
L124000	Mild or unspecified pre-eclampsia unspecified
L124100	Mild or unspecified pre-eclampsia - delivered
L124200	Mild or unspecified pre-eclampsia - delivered with p/

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Read code	Description
L124300	Mild or unspecified pre-eclampsia - not delivered
L124400	Mild or unspecified pre-eclampsia with p/n complication
L124500	Mild pre-eclampsia
L124600	Pre-eclampsia, unspecified
L124z00	Mild or unspecified pre-eclampsia NOS
L125.00	Severe pre-eclampsia
L125000	Severe pre-eclampsia unspecified
L125100	Severe pre-eclampsia - delivered
L125200	Severe pre-eclampsia - delivered with postnatal complication
L125300	Severe pre-eclampsia - not delivered
L125400	Severe pre-eclampsia with postnatal complication
L125z00	Severe pre-eclampsia NOS
L126.00	Eclampsia
L126000	Eclampsia unspecified
L126100	Eclampsia - delivered
L126200	Eclampsia - delivered with postnatal complication
L126300	Eclampsia - not delivered
L126400	Eclampsia with postnatal complication
L126500	Eclampsia in pregnancy
L126600	Eclampsia in labour
L126z00	Eclampsia NOS
L127.00	Pre-eclampsia or eclampsia with pre-existing hypertension
L127000	Pre-eclampsia or eclampsia with hypertension unspecified
L127100	Pre-eclampsia or eclampsia with hypertension – delivered
L127200	Pre-eclampsia or eclampsia with hypertension - del+p/
L127300	Pre-eclampsia or eclampsia with hypertension - not de
L127400	Pre-eclampsia or eclampsia with hypertension + p/n co
L127z00	Pre-eclampsia or eclampsia + pre-existing hypertension
L128.00	Pre-exist hypertension complications pregnancy childbirth and puer
L128000	Pre-exist hypertension heart disease complication pregnancy childbirth +puer
L128200	Pre-exist 2ndry hypertension complication pregnancy childbirth and puer
L129.00	Moderate pre-eclampsia
L12B.00	Proteinuric hypertension of pregnancy
L12z.00	Unspecified hypertension in pregnancy/childbirth/puer
L12z000	Unspecified hypertension in pregnancy/childbirth/puerperium unspecified
L12z100	Unspecified hypertension in pregnancy/childbirth/puerperium - delivered
L12z200	Unspecified hypertension in pregnancy/childbirth/puerperium -del +p
L12z300	Unspecified hypertension in pregnancy/childbirth/puerperium - not d
L12z400	Unspecified hypertension in pregnancy/childbirth/puerperium with p/
L12zz00	Unspecified hypertension in pregnancy/childbirth/puerperium NOS
Lyu1.00	[X]Oedema,proteinuria+hypertens in pregnancy, childbirth
TJC7.00	Adverse reaction to other antihypertensives
TJC7z00	Adverse reaction to antihypertensives NOS
U60C511	[X] Adverse reaction to other antihypertensives
U60C51A	[X] Adverse reaction to antihypertensives NOS

9.14 Read code list to identify perinatal death

Read code	Description
ZVu2C00	[X]Other multiple births, all stillborn
ZV27700	[V]Other multiple birth, all stillborn
ZV27400	[V]Twins, both stillborn
ZV27100	[V]Single stillbirth
ZV27.12	[V]Stillbirth
Q4z..15	Stillbirth NEC
Q4z..14	Perinatal death
Q4z..13	Newborn death
Q4z..12	Neonatal death
Q4z..11	Infant death
Q48y700	Late neonatal death
Q48y600	Early neonatal death
Q48D100	[X]Macerated stillbirth
Q48D000	[X]Fresh stillbirth
Q48D.00	[X] Stillbirth
Q211.00	Fetal death due to labour anoxia
Q210.00	Fetal death due to prelabour anoxia
L264z00	Intrauterine death NOS
L264200	Intrauterine death with antenatal problem
L264100	Intrauterine death - delivered
L264000	Intrauterine death unspecified
L264.11	Fetal death in utero
L264.00	Intrauterine death
6339.00	Triplets - 3 still born
6335.00	Twins - both still born
6332.00	Single stillbirth
633..12	Stillbirth [prevention record]
13MD.00	Death of child
13M2.00	Death of infant

9.15 Read code list to identify major congenital malformations

Read code	Description
P....00	Congenital anomalies
P00..00	Anencephalus
P000.00	Acrania
P1...00	Spina bifida
P10..00	Spina bifida with hydrocephalus
P101.00	Arnold - Chiari syndrome
P101000	Chiari malformation type I
P11..00	Spina bifida without mention of hydrocephalus
P113.00	Spinal meningocele
P114.00	Meningomyelocele
P114z00	Meningomyelocele NOS
P116.00	Myelocystocele
P117400	Sacral spina bifida without hydrocephalus - open
P20..00	Encephalocele
P20..12	Cephalocele
P20..15	Sinus pericranii
P203.00	Meningocele - cerebral
P20z000	Occipital encephalocele
P21..00	Microcephalus
P211.00	Micrencephaly
P220.00	Agenesis of brain, part unspecified
P223.11	Lissencephaly
P225.00	Holoprosencephaly
P226.00	Microgyria
P227100	Congenital hypoplasia of cerebrum
P228.00	Anomalies of corpus callosum
P228000	Congenital absence of corpus callosum
P228011	Agenesis of corpus callosum
P228100	Hypoplasia of corpus callosum
P229.00	Anomalies of hypothalamus
P22A.00	Anomalies of cerebellum
P22A100	Hypoplasia of cerebellum
P22y111	Joubert syndrome
P22y300	Partial absence of septum pellucidum
P22z.11	Cerebellar hypoplasia
P22z.13	Hypoplasia of part of brain NEC
P23..00	Congenital hydrocephalus
P233.11	Dandy - Walker syndrome
P240200	Schizencephaly
P241.11	Megalencephaly
P246.00	Septo-optic dysplasia

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Read code	Description
P248.00	Congenital dilated lateral ventricles of brain
P249.00	Megalencephaly
P250.00	Diastematomyelia
P2x2.00	Familial dysautonomia
P2x3.00	Jaw-winking syndrome
P2x4.00	Marcus - Gunn syndrome
P2x7.00	Congenital facial nerve palsy
P2y0.00	Congenital brain anomaly
P2y1.00	Congenital spinal cord anomaly
P2z..00	Nervous system anomalies NOS
P30..00	Anophthalmos
P300.00	Clinical anophthalmos, unspecified
P300200	Congenital absence of eye
P301.00	Congenital cystic eyeball
P30z.00	Anophthalmos NOS
P31..00	Microphthalmos
P310100	Hypoplasia of eye
P312.00	Microphthalmos with other eye anomaly
P32..00	Buphthalmos
P320000	Congenital glaucoma
P322100	Congenital megalocornea
P33..00	Congenital cataract and lens anomalies
P33..11	Congenital lens anomaly
P330.00	Congenital cataract, unspecified
P331100	Subcapsular cataract
P336200	Coloboma of lens
P33y000	Blue dot cataract
P340000	Microcornea
P340100	Congenital keratoconus
P341.00	Congenital corneal opacities
P341.11	Arcus juvenilis
P342100	Peter's anomaly
P343.00	Aniridia
P344000	Congenital anisocoria
P344200	Coloboma of iris
P350.00	Vitreous anomalies
P350000	Congenital vitreous opacity
P350z00	Vitreous anomalies NOS
P351.00	Fundus coloboma
P353000	Congenital folds of the posterior segment
P354.00	Congenital macular changes
P355000	Coloboma of retina
P355z00	Other congenital retinal changes NOS
P356.11	Optic disc congenital anomalies

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Read code	Description
P356000	Congenital optic disc coloboma
P358.00	Specified anomalies of choroid
P358000	Coloboma of choroid
P358z00	Specified anomaly of choroid NOS
P360.00	Congenital ptosis
P361400	Congenital blepharophimosis
P361500	Coloboma of eyelids
P362200	Fused eyelids
P363.00	Congenital lacrimal gland anomalies
P364.00	Congenital lacrimal passage anomalies
P36zz00	Eyelid, lacrimal system and orbit congenital anomalie
P37..00	Macrophthalmos
P3y0.00	Ocular albinism
P40..00	Ear anomalies with hearing impairment
P401.00	Congenital absence of external ear
P401000	Congenital absence of external ear, unspecified
P401100	Absence of external auditory canal
P402000	Atresia of external auditory canal
P405z00	Inner ear anomalies NOS
P40z.11	Deafness due to congenital anomaly NEC
P410.00	Supernumerary ear
P42..00	Other specified ear anomalies
P420.00	Congenital ear lobe absence
P423.00	Eustachian tube anomalies
P42zz00	Other ear anomalies NOS
P4y5.00	Mid-facial hypoplasia
P5...00	Bulbus cordis and cardiac septal closure anomalies
P5...11	Cardiac septal defects
P5...12	Congenital heart disease, septal and bulbar anomalies
P5...13	Heart septal defects
P50..00	Common aorto-pulmonary trunk
P500.12	Truncus arteriosus
P501.00	Aortic septal defect
P502.11	Truncus arteriosus
P51..00	Transposition of great vessels
P510.00	Total great vessel transposition
P511.00	Double outlet right ventricle
P512.00	Corrected great vessel transposition
P51y.00	Other specified transposition of great vessels
P51y.11	Transposition of aorta
P51z.00	Great vessel transposition NOS
P52..00	Tetralogy of Fallot
P520.00	Tetralogy of Fallot, unspecified
P520.11	Ventricular septal defect in Fallot's tetralogy

Continued on next page

Read code	Description
P54..00	Ventricular septal defect
P540.00	Ventricular septal defect, unspecified
P542.00	Left ventricle to right atrial communication
P54y.00	Other specified ventricular septal defect
P54z.00	Ventricular septal defect NOS
P55..00	Ostium secundum atrial septal defect
P550.00	Atrial septal defect NOS
P552.00	Persistent ostium secundum
P55y.00	Other specified ostium secundum atrial septal defect
P55y.11	Other specified atrial septal defect
P55z.00	Ostium secundum atrial septal defect NOS
P561.00	Ostium primum defect
P56z000	Common atrium
P56z200	Common atrioventricular-type ventricular septal defec
P58..00	Double outlet left ventricle
P59..00	Isomerism of atrial appendages
P5X..00	Congenital malforms of cardiac chambers+connections u
P6...00	Other congenital heart anomalies
P60..00	Pulmonary valve anomalies
P600.00	Pulmonary valve anomaly, unspecified
P601.00	Congenital atresia of the pulmonary valve
P601000	Hypoplasia of pulmonary valve
P602.00	Congenital pulmonary stenosis
P602z00	Congenital pulmonary stenosis NOS
P603.00	Right hypoplastic heart syndrome
P61..00	Congenital tricuspid atresia and stenosis
P610.00	Congenital tricuspid atresia
P62..00	Ebstein's anomaly
P63..00	Congenital aortic valve stenosis
P641.00	Bicuspid aortic valve
P67..00	Hypoplastic left heart syndrome
P68..00	Congenital heart disease
P6y..00	Other specified heart anomalies
P6y0.00	Subaortic stenosis
P6y1.00	Cor triatriatum
P6y2.00	Pulmonary infundibular stenosis
P6y3000	Uhl's disease
P6y4.00	Coronary artery anomaly
P6y5.00	Congenital heart block
P6y6000	Dextrocardia
P6y6200	Mesocardia
P6y6300	Ectopia cordis
P6y8.00	Congenital dextroposition of heart
P6yy.00	Other specified heart anomalies

Continued on next page

Read code	Description
P6yy.11	Hypoplastic aortic orifice or valve
P6yy.12	Hypoplasia of heart NOS
P6yy200	Congenital cardiomegaly
P6yy700	Atresia of heart valve NEC
P6yyz00	Other specified heart anomalies NOS
P6z..00	Congenital heart anomaly NOS
P6z..11	Chiari's malformation
P6z0.00	Unspecified anomaly of heart valve
P6z2.00	Acyanotic congenital heart disease NOS
P6z3.00	Cyanotic congenital heart disease NOS
P6z3.11	Blue baby
P6zz.00	Congenital heart anomaly NOS
P71..00	Coarctation of aorta
P710.00	Hypoplasia of aortic arch, unspecified
P71z.00	Coarctation of aorta NOS
P721.00	Aortic arch anomalies
P721111	Overriding aorta
P721200	Double aortic arch
P721600	Vascular ring, aorta
P721z00	Aortic arch anomalies NOS
P722200	Hypoplasia of aorta
P722400	Supra-valvular aortic stenosis
P722500	Atresia of aorta
P73..00	Pulmonary artery anomalies
P732.00	Pulmonary artery atresia
P733.00	Coarctation of the pulmonary artery
P734.00	Hypoplasia of the pulmonary artery
P737.11	Dilatation of pulmonary artery
P738.00	Atresia of pulmonary artery with septal defect
P73y.00	Other specified anomaly of pulmonary artery
P74..00	Anomalies of great veins
P741.00	Total anomalous pulmonary venous return - TAPVR
P741000	Subdiaphragmatic total anomalous pulmonary venous ret
P742.00	Partial anomalous pulmonary venous return
P74z600	Scimitar syndrome
P74z800	Atresia of pulmonary vein
P76..12	Other congenital anomalies of peripheral veins
P761.00	Anomaly of artery NEC
P766.00	Peripheral arterio-venous aneurysm
P766.11	Peripheral arterio-venous malformation
P768.00	Congenital phlebectasia
P76C.00	Anomalies of renal artery NEC
P76D.00	Arteriovenous malformation
P76yz00	Other congenital anomaly of peripheral vascular syste

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Read code	Description
P7X..00	Congenital malformation of great arteries, unspecifie
P7y0112	Congenital cerebral arteriovenous malformation
P7y0400	Vein of Galen malformation
P7yz100	Congenital chylothorax
P7z..00	Circulatory system anomaly NOS
P8...00	Respiratory system congenital anomalies
P80..00	Choanal atresia
P800.00	Choanal atresia, unspecified
P813.00	Congenital cleft nose
P814.00	Deformity of nasal sinus wall
P817.00	Perforated nasal septum
P81z.11	Single nostril
P831100	Anomaly of epiglottis
P831500	Laryngeal hypoplasia
P83y300	Congenital laryngocele
P83yB00	Congenital bronchomalacia
P83yX00	Congenital malformation of larynx, unspecified
P84..00	Congenital cystic lung
P840.00	Congenital cystic lung disease, unspecified
P843.00	Single lung cyst
P843.11	Lung cyst
P843.12	Congenital bronchogenic cyst
P844.00	Congenital cystic adenomatoid malformation of the lun
P84y.00	Other specified congenital cystic lung
P84z.00	Congenital cystic lung NOS
P85..00	Lung agenesis, hypoplasia and dysplasia
P851.00	Hypoplasia of lung
P852.00	Sequestration of lung
P853.00	Agenesis of lung
P86..00	Other lung anomalies
P86y.00	Other lung anomaly
P86yz00	Other lung anomaly NOS
P86z.00	Lung anomaly NOS
P9...00	Cleft palate and lip
P90..00	Cleft palate
P900.00	Cleft palate, unspecified
P903.00	Bilateral complete cleft palate
P906.00	Central incomplete cleft palate
P906.11	Cleft soft palate, central
P907.00	Complete cleft palate NOS
P907.11	Cleft hard palate NOS
P908.00	Incomplete cleft palate NOS
P908.11	Cleft soft palate NOS
P909.00	Cleft uvula

Continued on next page

Read code	Description
P90A.00	Cleft soft palate, bilateral
P90z.00	Cleft palate NOS
P91..00	Cleft lip (harelip)
P91..11	Cheiloschisis
P910.00	Cleft lip, unspecified
P911.00	Unilateral complete cleft lip
P912.00	Unilateral incomplete cleft lip
P914.00	Bilateral incomplete cleft lip
P91z.00	Cleft lip NOS
P92..00	Cleft palate with cleft lip
P921.00	Unilateral complete cleft palate with cleft lip
P923.00	Bilateral complete cleft palate with cleft lip
P928.00	Cleft hard palate with cleft soft palate, unilateral
P92B.00	Cleft hard palate with cleft lip, unilateral
PA24.11	Congenital pits of lip
PA25000	Congenital absence of uvula
PA25y00	Other congenital anomaly of palate
PA26.11	Pharyngeal pouch
PA27100	Congenital pharyngeal polyp
PA29.00	Other anomalies of salivary glands or ducts
PA2A.00	Other anomalies of lip
PA2Az00	Other anomaly of lip NOS
PA30.00	Atresia of oesophagus
PA31.00	Congenital oesophageal stricture
PA31.11	Congenital oesophageal stenosis
PA32.00	Congenital oesophageal fistula
PA32111	Congenital tracheo-oesophageal fistula
PA37.00	Atresia of oesophagus with tracheo-oesophageal fistul
PA3y.00	Other specified oesophageal atresia, stenosis or fist
PA5..00	Congenital hypertrophic pyloric stenosis
PA7..00	Other specified stomach anomalies
PA76.00	Microgastria
PA77.00	Transposition of stomach
PAz0.00	Unspecified anomalies of mouth and pharynx
PAz2.00	Unspecified anomalies of stomach
PB03.11	Persistent vitelline duct
PB10.00	Atresia of small intestine
PB10100	Atresia of duodenum
PB10200	Atresia of ileum
PB10300	Atresia of jejunum
PB2..11	Atresia large intestine
PB2..12	Stenosis large intestine
PB20400	Congenital absence of rectum with fistula
PB21100	Atresia of colon

Continued on next page

Read code	Description
PB21200	Atresia of rectum
PB23.00	Congenital occlusion of anus
PB23000	Congenital occlusion of anus with fistula
PB23z00	Congenital occlusion of anus NOS
PB24.11	Congenital anal stricture
PB24111	Congenital stenosis of anus without mention of fistul
PB25.00	Congenital stricture of rectum
PB26.00	Imperforate anus
PB26000	Imperforate anus with fistula
PB26z00	Imperforate anus NOS
PB30.00	Hirschsprung's disease
PB30z00	Hirschsprung's disease NOS
PB33.00	Total intestinal aganglionosis
PB40.00	Congenital intestinal adhesions
PB41.00	Malrotation of colon and caecum
PB4z.12	Malrotation of gut
PB4z.13	Malrotation of intestine
PB53200	Transposition of caecum
PB54.00	Ectopic anus
PB57.00	Microcolon
PB59.00	Congenital anal fistula
PB5X.00	Congenital malformation of intestine, unspecified
PB5z.12	Short bowel syndrome
PB6..12	Biliary anomalies
PB6..13	Gallbladder anomalies
PB6..14	Liver anomalies
PB61.00	Biliary atresia
PB62.00	Congenital cystic liver disease
PB63300	Riedel's lobe liver
PB63500	Alagille syndrome
PB6y900	Liver hyperplasia
PB6yw11	Liver hamartoma
PBy2.00	Congenital malposition of digestive system NOS
PBz..00	Digestive system anomalies NOS
PC00.00	Congenital absence of ovary
PC11100	Fimbrial cyst
PC11200	Gartner's duct cyst
PC11300	Parovarian cyst
PC2..00	Doubling of uterus
PC20.00	Doubling of uterus, unspecified
PC21.00	Didelphic uterus
PC3..00	Other anomalies of uterus
PC33.00	Bicornuate uterus
PC34.00	Uterus unicornis

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Read code	Description
PC35.00	Displaced uterus
PC35.11	Congenital prolapse of uterus
PC36z00	Fistula involving uterus with digestive or urinary tr
PC3z.00	Anomalies of uterus NOS
PC41000	Congenital cyst of canal of Nuck
PC43.00	Rectovaginal fistula, congenital
PC4yB00	Atresia of vagina
PC4yB11	Imperforate vagina
PC4yC00	Congenital vaginal cyst NEC
PC4yD00	Fusion of vulva
PC4yw00	Other congenital anomaly of vagina
PC4yw11	Vaginal septum
PC4yz00	Other cervical/vaginal/external female genital anomal
PC6..00	Hypospadias and epispadias
PC60.00	Hypospadias
PC60000	Hypospadias, penile
PC60100	Hypospadias, penoscrotal
PC60200	Hypospadias, perineal
PC60311	Hypospadias, glanular
PC60312	Hypospadias, glandular
PC61.00	Epispadias
PC62.00	Congenital chordee
PC8..00	Congenital anomaly of male genital system
PC80.00	Other specified congenital anomaly of male genital sy
PCy..00	Other specified genital organ anomaly
PCy1200	Congenital aplasia of testicle
PCy2100	Hypoplasia of testis
PCy2200	Hypoplasia of scrotum
PCy4.11	Congenital absence of both testes
PCy5.11	Congenital absence of testis, unilateral
PCyA200	Hydatid cyst of Morgagni - male
PCyA700	Cyst of embryonic remnant - female
PCyB.00	Doubling of vagina
PCyw.00	Other congenital anomaly of testis or scrotum
PCyy.00	Other congenital anomaly of penis
PCyz.00	Other specified genital organ anomaly NOS
PCz..00	Genital organ anomaly NOS
PD...00	Urinary system congenital anomalies
PD0..00	Renal agenesis and dysgenesis
PD00.00	Renal agenesis, unspecified
PD00100	Unilateral renal agenesis
PD01.00	Congenital renal atrophy
PD02.00	Congenital absence of kidney
PD02100	Unilateral congenital absence of kidney

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Read code	Description
PD03.00	Hypoplasia of kidney
PD03000	Bilateral renal hypoplasia
PD03011	Potter's syndrome
PD04.00	Dysplasia of kidney
PD04000	Bilateral renal dysplasia
PD04100	Unilateral renal dysplasia
PD04z00	Dysplasia of kidney NOS
PD0z.00	Renal agenesis or dysgenesis NOS
PD1..00	Congenital cystic kidney disease
PD1..11	Congenital cystic renal disease
PD1..13	Polycystic kidney
PD1..14	Sponge kidney
PD11.00	Polycystic kidney disease
PD11000	Polycystic kidneys, infantile type
PD11100	Polycystic kidneys, adult type
PD11z11	Cystic kidney disease NEC
PD12111	Medullary sponge kidney
PD13.00	Multicystic renal dysplasia
PD13.11	Multicystic kidney
PD1z.00	Congenital cystic kidney disease NOS
PD2..00	Renal pelvis and ureter obstructive defects
PD22.00	Congenital stricture of ureter
PD23.00	Congenital hydronephrosis
PD23.11	Congenital dilated renal pelvis
PD24.00	Congenital dilatation of ureter
PD25.00	Hydroureter - congenital
PD26.00	Megaloureter - congenital
PD27.00	Ureterocele - congenital
PD2y.00	Other specified obstructive defect of renal pelvis or
PD2z.00	Obstructive defect of renal pelvis or ureter NOS
PD3..00	Other specified renal anomaly
PD34.00	Double kidney with double pelvis
PD34.11	Duplex kidneys
PD35.00	Ectopic kidney
PD35.11	Pelvic kidney
PD36.00	Fusion of kidneys
PD38.00	Horseshoe kidney
PD3A.00	Lobulation of kidney
PD3D.00	Enlarged kidney
PD3z.00	Other specified renal anomaly NOS
PD44.00	Double ureter
PD45.00	Ectopic ureter
PD46.00	Anomalous ureter implantation
PD4z.00	Other specified ureter anomaly NOS

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Read code	Description
PD5..00	Exstrophy of urinary bladder
PD50.00	Ectopic bladder
PD50.11	Ectopia vesicae
PD5z.00	Exstrophy of urinary bladder NOS
PD60.00	Congenital bladder neck obstruction
PD61.00	Congenital obstruction of urethra
PD61100	Stenosis of anterior urethra
PD62.00	Congenital urethral valvular stricture
PD63.00	Congenital urinary meatus stricture
PD63.12	Congenital pinhole urinary meatus
PD65.00	Imperforate urinary meatus
PD67.00	Congenital posterior urethral valves
PD7..00	Anomalies of urachus
PD70.00	Cyst of urachus
PD72.00	Patent urachus
PD73.00	Persistent umbilical sinus
PDy3.00	Accessory urethra
PDy4.00	Congenital bladder diverticulum
PDy7.00	Congenital prolapse of bladder mucosa
PDyA.00	Double urinary meatus
PDyz.00	Other bladder or urethral anomaly NOS
PDyz000	Epispadias, female
PDz..00	Urinary system anomalies NOS
PDz0.00	Unspecified anomaly of kidney
PDz3.00	Unspecified anomaly of urethra
PE...11	Congenital musculoskeletal deformities
PE0..12	Jaw congenital deformities
PE00000	Hemifacial microsomia
PE1..11	Congenital wry neck
PE1..12	Sternomastoid tumour
PE23.00	Congenital scoliosis due to congenital bony malformat
PE8y000	Congenital club hand
PE8y600	Congenital flexion contracture of hip
PE8y700	Congenital abduction contracture of hip
PE9..11	Other congenital musculoskeletal deformity
PF...00	Other congenital limb anomalies
PF0..00	Polydactyly - supernumerary digits
PF00.00	Supernumerary digits, unspecified
PF01.00	Accessory fingers
PF01000	Radial polydactyly Wassel 1
PF01300	Radial polydactyly Wassel 4
PF01800	Ulnar polydactyly
PF02.00	Accessory toes
PF02100	Accessory little toe

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Read code	Description
PF02200	Other accessory toe
PF03.00	Accessory thumbs
PF0z.00	Polydactyly NOS
PF1..00	Syndactyly - webbing of digits
PF10.00	Syndactyly of multiple digits, unspecified
PF11.00	Syndactyly of fingers without bone fusion
PF11.11	Webbed fingers
PF11100	Simple syndactyly - 2nd to 4th web
PF12.11	Fused fingers
PF13.11	Webbed toes
PF14.11	Fused toes
PF14.12	Conjoined toes
PF15.00	Polysyndactyly
PF1z.12	Symphalangism
PF20200	Hemimelia of upper limb NOS
PF21.00	Transverse deficiency of arm
PF21400	Congenital amputation of upper limb
PF22000	Phocomelia of upper limb NOS
PF26.00	Agenesis of radial ray
PF26.11	Congenital absence of radius
PF26300	Absent thumb
PF28.00	Agenesis of carpals and metacarpals
PF28.11	Transverse arrest of carpals and metacarpals
PF29.00	Congenital absence of finger
PF29.11	Ectrodactyly of finger
PF29z00	Congenital absence finger NOS
PF2y.00	Other specified reduction deformities of upper limb
PF2z.11	Hypoplasia of upper limb
PF3..00	Reduction deformity of lower limb
PF30.00	Congenital shortening of leg, unspecified
PF30100	Hemimelia of lower limb NOS
PF37.00	Agenesis of fibula
PF39.00	Congenital absence of toe
PF3A.00	Split foot
PF44.00	Phocomelia of unspecified limb
PF46.00	Longitudinal reduction deformity of unspecified limb
PF47.00	Congenital absence of digits NOS
PF4z.11	Brachydactyly NOS
PF4z.13	Hypoplasia of limb NOS
PF50.00	Upper limb anomaly, unspecified
PF51.00	Congenital deformity of clavicle
PF54.00	Madelung's deformity
PF55000	Acrocephalosyndactyly (Apert)
PF55300	Saethre-Chotzen syndrome

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Read code	Description
PF58.00	Congenital cleft hand
PF58.11	Lobster-claw hand
PF58200	Cleft hand with syndactyly
PF59000	Windblown hand
PF59500	Thumb in palm deformity
PF59600	Congenital trigger thumb
PF5B.00	Other duplication of limb
PF5Bz00	Duplication of limb NOS
PF5E.00	Constriction ring syndrome of upper limb
PF5E200	Acrosyndactyly
PF5G.00	Congenital complete absence of upper limb(s)
PF5r.00	Other congenital anomalies of fingers
PF5r000	Triphalangeal thumb
PF5r200	Camptodactyly
PF5r400	Flexion deformity of fingers
PF5r700	Symbrachydactyly
PF5r800	Camptodactyly-little finger
PF5rD00	Congenital malformation of thumb
PF5s.00	Other congenital anomalies of hand
PF5u.00	Other congenital anomalies of forearm
PF5uz00	Other congenital anomaly forearm NOS
PF5v.00	Congenital anomalies of elbow and upper arm
PF5w.11	Congenital deformity of scapula NEC
PF5y000	Cleidocranial dysostosis
PF5z.00	Upper limb or shoulder anomaly NOS
PF60.00	Lower limb anomaly, unspecified
PF62.00	Congenital coxa vara
PF6x.00	Other congenital anomalies of pelvis
PG02.00	Congenital forehead deformity
PG03.00	Craniosynostosis
PG03.11	Scaphocephaly
PG03000	Muenke syndrome
PG04.00	Craniofacial dysostosis
PG04.11	Crouzon's disease
PG06.00	Imperfect fusion of skull
PG07.00	Oxycephaly
PG08.00	Platybasia
PG09.00	Premature cranial suture closure
PG0B.00	Trigonocephaly
PG0C.00	Pierre - Robin syndrome
PG0F.00	Goldenhar's syndrome
PG0G.00	Localised skull defects
PG0y.11	Defect of skull ossification
PG0y000	Brachycephaly

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Read code	Description
PG0z.11	Dysmorphic features
PG1..00	Anomalies of spine
PG10.00	Anomaly of spine, unspecified
PG12.00	Congenital spondylolisthesis
PG14.00	Hemivertebra
PG14100	Thoracic hemivertebra
PG14z00	Hemivertebra NOS
PG16.00	Klippel-Feil syndrome
PG18.00	Congenital kyphosis
PG18.11	Congenital kyphoscoliosis
PG1x.00	Congenital sacrococcygeal anomalies NEC
PG1y400	Hypoplasia of spine
PG3..00	Other rib and sternum anomalies
PG31.00	Congenital absence of sternum
PG35.00	Mis-shapen ribs
PG4..00	Chondrodysplasia
PG41.00	Achondroplasia
PG41.11	Dwarfism
PG42.00	Multiple enchondromata
PG42.15	Hypochondroplasia
PG42011	Kast's syndrome
PG43.00	Asphyxiating thoracic dysplasia
PG43.11	Jeune's syndrome
PG44200	Thanatophoric dwarfism
PG46.00	Spondyloepiphyseal dysplasia
PG47.00	Congenital exostosis
PG4B000	Achondrogenesis
PG4C.00	Chondrodysplasia punctata
PG51.00	Osteogenesis imperfecta
PG51.12	Eddowe's syndrome
PG51.16	Brittle bone disease
PG53.00	Osteopoikilosis
PG54.00	Polyostotic fibrous dysplasia
PG56.00	Multiple epiphyseal dysplasia
PG57.11	Caffey's syndrome
PG5B.00	Multiple synostosis syndrome
PG5D.00	Craniodiaphyseal dysplasia
PG6..00	Anomalies of diaphragm
PG61.00	Congenital diaphragmatic hernia
PG63.00	Eventration of diaphragm
PG7..00	Abdominal wall anomalies
PG70.00	Exomphalos
PG71.00	Gastroschisis
PG72.00	Prune belly syndrome

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Read code	Description
PG7y.00	Other specified anomaly of abdominal wall
PG7z.00	Abdominal wall anomaly NOS
PGX..00	Congenital malformation of bony thorax, unspecified
PGy0.00	Congenital absence of muscle and tendon
PGy0100	Poland's syndrome
PGy2.00	Ehlers-Danlos syndrome
PGy2200	Ehlers-Danlos syndrome type III
PGy3.00	Nail-patella syndrome
PGy3.11	Osteo-onychodysostosis
PGyy200	Hypoplasia of muscle
PGyy400	Aplasia of muscle
PH00.00	Congenital lymphoedema
PH02.00	Milroy's disease
PH02.11	Meige's disease
PH1..00	Ichthyosis congenita
PH11.00	Harlequin fetus
PH12.00	Ichthyosiform erythroderma
PH12.11	Sjogren - Larsson syndrome
PH13.00	Collodion baby
PH14.00	Ichthyosis vulgaris
PH1y000	Netherton's syndrome
PH30.00	Congenital ectodermal dysplasia
PH31.00	Vascular hamartomas
PH31.11	Vascular naevus
PH32100	Urticaria pigmentosa
PH32112	Mastocytosis
PH32300	Incontinentia pigmenti
PH32311	Bloch - Sulzberger syndrome
PH32z00	Congenital pigmentary skin anomaly NOS
PH33100	Hailey-Hailey disease
PH33300	Rothmund-Thomson syndrome
PH33500	Pseudoxanthoma elasticum
PH33511	Darier's disease - pseudoxanthoma elasticum
PH3y200	Epidermolysis bullosa
PH3y212	Koebner's disease
PH3y300	Congenital keratoderma
PH3y400	Congenital keratosis follicularis
PH3y411	Darier's disease - keratosis follicularis
PH3y500	Acanthosis nigricans, congenital
PH3y600	Keratosis palmaris et plantaris
PH3y611	Tylosis palmaris et plantaris
PH3y700	Epidermolysis bullosa simplex
PH3y900	Epidermolysis bullosa dystrophica
PH3yz00	Other congenital skin anomaly NOS

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Read code	Description
PH40.00	Congenital alopecia
PH60.00	Absent breast
PH62.00	Accessory breast
PH66.00	Hypoplasia of breast
PH68.00	Ectopic breast tissue
PH7..00	Cutis marmorata telangiectasia congenita
PHz..00	Integument anomalies NOS
PHz0.00	Unspecified congenital anomalies of skin
PJ21.00	Trisomy 18, mosaicism
PJ37.12	Autosomal deletion - mosaicism
PJ50.00	Whole chromosome trisomy syndromes
PJ52.00	Trisomies of autosomes NEC
PJz3.00	Duplication of chromosome
PK0..00	Anomalies of spleen
PK01.00	Absent spleen
PK01.11	Asplenia
PK03.00	Congenital splenomegaly
PK0z.00	Anomalies of spleen NOS
PK1..00	Anomalies of adrenal gland
PK23.00	Thyroglossal duct cyst
PK24.00	Anomalies of pituitary gland
PK25.00	Anomalies of thyroid gland NEC
PK26.00	Anomalies of thyroglossal duct NEC
PK28100	Congenital absence of thymus
PK3..00	Situs inversus
PK30.00	Situs inversus, unspecified
PK31.00	Situs inversus abdominalis
PK35.00	Kartagener's syndrome
PK5..00	Tuberous sclerosis
PK60.00	Peutz - Jegher's syndrome
PK61.00	Sturge-Weber syndrome
PK62.00	Von Hippel-Lindau syndrome
PK80.00	Fetal alcohol syndrome
PK84.00	Fetal valproate syndrome
PKy2.00	Marfan's syndrome
PKy4.00	William syndrome
PKy5.00	Congen malformation syndromes affecting facial appear
PKy5400	Waardenburg's syndrome
PKy5500	Gorlin-Chaudhry-Moss syndrome
PKy5C00	Treacher Collins syndrome
PKy5D00	Kabuki make-up syndrome
PKy5E00	Branchio-otorenal dysplasia
PKy6.00	Congenital malformation syndromes with short stature
PKy6011	Cornelia de Lange syndrome

Continued on next page

Read code	Description
PKy6200	Russell - Silver syndrome
PKy7100	Holt - Oram syndrome
PKy7200	Klippel - Trenaunay - Weber syndrome
PKy7500	Arachnodactyly
PKy7B00	Stickler syndrome
PKy8000	Noonan's syndrome
PKy9100	Beckwith's syndrome
PKy9111	Wiedemann - Beckwith syndrome
PKy9200	Menke's syndrome
PKy9300	Prader - Willi syndrome
PKy9400	Zellweger's syndrome
PKy9600	VATER association
PKyz600	Congenital hemihypertrophy
Py...00	Other specified congenital anomaly
Pyu4100	[X]Unspecified cleft palate with cleft lip, bilateral
Pyu9D00	[X]Primary ciliary dyskinesia
PyuAC00	[X]Townes-Brocks syndrome
Pz...00	Congenital anomaly NOS

Appendix IV. Univariate Poisson regression

9.16 Univariate Poisson regression of association between diabetes type and maternal characteristics

		Type 1 diabetes		Type 2 diabetes	
		RR (95% CI)	p-value	RR (95% CI)	p-value
Age	10 years	1.13 (1.02, 1.25)	0.02	2.14 (1.95, 2.34)	<0.001
Diastolic blood pressure	10 mmHg	1.16 (1.08, 1.24)	<0.001	1.61 (1.52, 1.70)	<0.001
Age	16-24	-	0.6	-	<0.001
	25-34	1.13 (0.88, 1.45)		6.29 (3.90, 10.15)	
	35+	1.10 (0.72, 1.70)		12.14 (7.22, 20.42)	
Townsend	1	-	0.8	-	<0.001
	2	1.03 (0.86, 1.24)		1.26 (1.05, 1.51)	
	3	0.93 (0.77, 1.12)		1.60 (1.35, 1.89)	
	4	0.97 (0.81, 1.17)		1.56 (1.32, 1.85)	
	5	0.93 (0.76, 1.14)		1.78 (1.50, 2.12)	
Smoking status	Never	-	0.8	-	<0.001
	Former	1.02 (0.89, 1.19)		1.03 (0.91, 1.15)	
	Current	0.97 (0.83, 1.12)		0.77 (0.67, 0.87)	
Alcohol dependence	No	-	0.006	-	0.7
	Yes	2.48 (1.40, 4.38)		0.87 (0.39, 1.93)	
Hyperglycaemia	No	-	<0.001	-	<0.001
	Yes	503.59 (446.34)		211.76 (187.30, 239.41)	
Overweight	No	-	0.002	-	<0.001
	Yes	0.83 (0.73, 0.93)		2.49 (2.19, 2.82)	

9.17 Univariate Poisson regression of association between each outcome and maternal characteristic

Caesarean section delivery

		RR (95% CI)	p-value
Age	10 years	1.49 (1.47, 1.51)	<0.001
Diastolic blood pressure	10 mmHg	1.14 (1.12, 1.15)	<0.001
Age	16-24	-	<0.001
	25-34	1.66 (1.59, 1.73)	
	35+	2.62 (2.48, 2.77)	
Townsend	1	-	<0.001
	2	0.99 (0.96, 1.01)	
	3	0.96 (0.94, 0.99)	
	4	0.93 (0.91, 0.96)	
	5	0.92 (0.89, 0.95)	
Smoking status	Never	-	<0.001
	Former	1.02 (1.00, 1.04)	
	Current	0.91 (0.89, 0.93)	
Alcohol dependence	No	-	0.4
	Yes	0.95 (0.84, 1.08)	
Hyperglycaemia	No	-	<0.001
	Yes	2.93 (2.68, 3.20)	
Overweight	No	-	<0.001
	Yes	1.25 (1.23, 1.28)	

Instrumental delivery

		RR (95% CI)	p-value
Age	10 years	0.91 (0.89, 0.93)	<0.001
Diastolic blood pressure	10 mmHg	1.00 (0.98, 1.02)	0.997
Age	16-24	-	<0.001
	25-34	0.92 (0.87, 0.97)	
	35+	0.70 (0.63, 0.78)	
Townsend	1	-	<0.001
	2	0.99 (0.95, 1.03)	
	3	0.95 (0.91, 0.99)	
	4	0.85 (0.81, 0.88)	
	5	0.82 (0.78, 0.86)	
Smoking status	Never	-	<0.001
	Former	0.94 (0.91, 0.97)	
	Current	0.84 (0.81, 0.87)	
Alcohol dependence	No	-	0.8
	Yes	0.98 (0.80, 1.20)	
Hyperglycaemia	No	-	0.2
	Yes	0.84 (0.64, 1.10)	
Overweight	No	-	<0.001
	Yes	0.84 (0.81, 0.86)	

Preeclampsia

		RR (95% CI)	p-value
Age	10 years	0.89 (0.81, 0.98)	0.02
Diastolic blood pressure	10 mmHg	1.08 (1.00, 1.18)	0.05
Age	16-24	-	<0.001
	25-34	0.68 (0.56, 0.83)	
	35+	0.96 (0.68, 1.36)	
Townsend	1	-	0.3
	2	0.97 (0.81, 1.16)	
	3	0.98 (0.82, 1.16)	
	4	0.85 (0.71, 1.02)	
	5	0.86 (0.70, 1.04)	
Smoking status	Never	-	<0.001
	Former	0.98 (0.86, 1.12)	
	Current	0.70 (0.60, 0.82)	
Alcohol dependence	No	-	0.8
	Yes	1.13 (0.51, 2.52)	
Hyperglycaemia	No	-	0.01
	Yes	2.59 (1.34, 4.99)	
Overweight	No	-	0.8
	Yes	1.01 (0.90, 1.14)	

Perinatal death

		RR (95% CI)	p-value
Age	10 years	1.16 (1.05, 1.28)	0.004
Diastolic blood pressure	10 mmHg	1.11 (1.03, 1.19)	0.006
Age	16-24	-	0.005
	25-34	0.78 (0.62, 0.95)	
	35+	1.27 (0.91, 1.79)	
Townsend	1	-	<0.001
	2	1.09 (0.89, 1.32)	
	3	1.10 (0.91, 1.34)	
	4	1.29 (1.07, 1.56)	
	5	1.53 (1.26, 1.85)	
Smoking status	Never	-	<0.001
	Former	0.79 (0.68, 0.92)	
	Current	1.30 (1.13, 1.49)	
Alcohol dependence	No	-	0.02
	Yes	2.16 (1.19, 3.92)	
Hyperglycaemia	No	-	<0.001
	Yes	3.60 (2.04, 6.37)	
Overweight	No	-	0.01
	Yes	1.18 (1.04, 1.33)	

Major congenital malformations

		RR (95% CI)	p-value
Age	10 years	1.06 (1.01, 1.11)	0.02
Diastolic blood pressure	10 mmHg	1.03 (0.99, 1.07)	0.1
Age	16-24	-	0.02
	25-34	0.98 (0.87, 1.09)	
	35+	1.23 (1.02, 1.48)	
Townsend	1	-	0.5
	2	1.00 (0.91, 1.10)	
	3	1.05 (0.96, 1.15)	
	4	1.06 (0.97, 1.16)	
	5	1.05 (0.95, 1.15)	
Smoking status	Never	-	0.06
	Former	1.07 (1.00, 1.15)	
	Current	1.08 (1.00, 1.15)	
Alcohol dependence	No	-	0.09
	Yes	1.39 (0.97, 1.99)	
Hyperglycaemia	No	-	<0.001
	Yes	3.34 (2.51, 4.45)	
Overweight	No	-	0.3
	Yes	1.03 (0.97, 1.10)	

Appendix V - Publications arising from the PhD

Open Access Research

BMJ Open

A cohort study of trends in the prevalence of pregestational diabetes in pregnancy recorded in UK general practice between 1995 and 2012

Sonia J Coton, Irwin Nazareth, Irene Petersen

To cite: Coton SJ, Nazareth I, Petersen I. A cohort study of trends in the prevalence of pregestational diabetes in pregnancy recorded in UK general practice between 1995 and 2012. *BMJ Open* 2016;6:e009494. doi:10.1136/bmjopen-2015-009494

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2015-009494).

Received 22 July 2015
Revised 12 November 2015
Accepted 10 December 2015

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ABSTRACT

Objective: To describe the characteristics of pregnant women with and without pregestational diabetes and to estimate the prevalence of pregestational diabetes in pregnant women recorded in a UK primary care database.

Methods: The data source for this study is The Health Improvement Network (THIN) primary care database. Pregnant women with and without diabetes aged 16 years and over were identified using diagnostic Read codes and prescriptions for antidiabetics from medical records. Data were examined on: age, body mass index (BMI), social deprivation, smoking, ethnicity and glycaemic control. The prevalence of pregestational diabetes was calculated by diabetes type and calendar year between 1995 and 2012.

Results: Data from 400 434 pregnancies suggests that women with pregestational diabetes were: older (median 29, 32 vs 29 years for type 1, type 2 and without diabetes, respectively), had higher BMI (median 25.0, 30.4 vs 23.9 k/m^2 for type 1, type 2 and without diabetes, respectively) and were registered with a general practice for longer than pregnant women without diabetes. The prevalence of type 1 diabetes in pregnancy increased from 1.56 to 4.09 per 1000 pregnancies between 1995 and 2015. For type 2 diabetes the increase was from 2.34 to 5.09 per 1000 pregnancies between 1995 and 2008 followed by a more rapid increase to 10.62 per 1000 pregnancies by 2012.

Conclusions: Pregnant women with pregestational diabetes were older, had higher BMI and were registered for longer than women without diabetes. The prevalence of type 1 and type 2 diabetes increased in pregnancy. The prevalence of type 2 diabetes rose more rapidly with a marked increase after 2008.

Strengths and limitations of this study

- This study is one of the most comprehensive studies of the prevalence of pregestational diabetes in pregnancy, based on electronic health records in the UK.
- The data source for this study was a large primary care database that is representative of the UK population with over 3 million active patients.
- The study only captures individuals who have been diagnosed with diabetes in primary care as the primary reason for data collection is patient care and management not research.

INTRODUCTION

Diabetes mellitus is a chronic metabolic disease caused by a decrease in the production of insulin or sensitivity to insulin. Type 1 diabetes is caused by the destruction of insulin producing cells in the pancreas and is most commonly diagnosed in childhood. Type 2 diabetes is caused by cells insensitivity to insulin and insufficient production of insulin. Type 2 diabetes is more common among adults, although it is becoming increasingly prevalent in adolescents.[1]

Pregestational diabetes is one of the commonest chronic conditions affecting pregnancy; in the UK 1 in every 250 pregnancies is complicated by pregestational diabetes.[2] And the prevalence is increasing, in the UK the prevalence of pregestational diabetes increased from 3.1 to 4.7 per 1000 births between 1996–1998 and 2002–2004.[3]

Diabetes in pregnancy is associated with increased risk of pregnancy complications and adverse birth outcomes. Pregnancies affected by pregestational diabetes are at an increased risk of spontaneous abortion, caesarean section, congenital anomalies and perinatal mortality.[3–7]

The current literature on the prevalence of diabetes in pregnancy is based on regional or national samples selected from hospitals, maternity units or small community-based samples.[5 8 9] We used data from UK primary care records dating back to the 1990s.

The aims of this study were to examine characteristics of pregnant women with and

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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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http://dx.doi.org/10.2147/CLEP.S113413